Local Anesthetics That Metabolize to 2,6-Xylidine or *o*-Toluidine

Final Review of Toxicological Literature

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Integrated Laboratory Systems

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Final Review of Toxicological Literature

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EXECUTIVE SUMMARY

The nomination of amide local anesthetics by a private individual is based on their widespread use in dentistry, general medicine, surgery, and in some consumer products (e.g., topical skin preparations). The amide local anesthetics bupivacaine, etidocaine, lidocaine, mepivacaine, and ropivacaine metabolize to 2,6-xylidine and 4-hydroxyxylidine. Prilocaine metabolizes to *o*-toluidine. Both 2,6-xylidine and *o*-toluidine have been shown to be carcinogenic in laboratory animals in NTP studies. Two other amide local anesthetics, pyrrocaine and trimecaine, that were considered for inclusion in this report were excluded after it was found that they are not used in the United States. For these reasons, the local anesthetics reviewed in this report are bupivacaine, etidocaine, lidocaine, mepivacaine, prilocaine, and ropivacaine.

Production, Use, and Exposure

There is no information available for the production volume of the amide local anesthetics. In 1990, U.S. sales of the injectable local anesthetics Xylocaine® (lidocaine hydrochloride) and Marcaine® (bupivacaine hydrochloride) were 22.5 million and 10.7 million dollars, respectively.

The amide local anesthetics block axonal nerve conduction by reaching the nerve axon and interfering with the function of the ion channels that control nerve impulse propagation. The amide local anesthetics are used intravenously, epidurally, topically, or subcutaneously to relieve pain during and after medical procedures. Lidocaine is also used as an antiarrhythmic agent. Long-acting, epidurally infused anesthetics such as bupivacaine and mepivacaine are becoming increasingly used in obstetrics and post-surgical management of pain. Topically applied anesthetics are used in dentistry and management of pain in the skin (e.g., burns, shingles). Lidocaine, in topical formulations for the treatment of skin irritation, is the only amide local anesthetic available over the counter.

Epidurally, intravenously, or subcutaneously administered amide local anesthetics would most likely result in acute exposure unless used for the management of pain during extensive, repeated dental or medical treatment. Epidural use of the long-acting local anesthetics such as bupivacaine and lidocaine can result in infusion periods of 96 hours for management of postoperative pain. Chronic use of lidocaine may occur from topical application to manage pain due to skin conditions such as shingles or burns. The exposure of the fetus to epidural local anesthetics given to the mother during delivery may be substantial. Studies with bupivacaine show that cord venous/maternal venous plasma concentration ratios of total bupivacaine are about 0.5; however, cord/maternal venous plasma ratios of unbound bupivacaine may be higher (>1) due to low protein binding in the fetus. Also, excretion of long-acting epidural anesthetics and their metabolites in neonates may persist for up to three days after delivery.

Analytical Determination

Analytical methods for determining amide local anesthetics and their metabolites in biological matrices and pharmaceutical preparations are described in some detail in Appendix J. In the 1970s and 1980s, packed-column gas chromatography (GC) methods predominated over capillary GC and HPLC (with ultraviolet detectors) methods. Packed-GC methods with

detection by mass spectrometry (MS), flame ionization detectors (FID), and nitrogen (N)-FID had sensitivities of at least 2.5 ng/mL (but usually greater than 20 ng/mL). Since the mid-1980s, capillary GC and HPLC have become more common. In the 1980s, capillary GC with detection by N-FID or MS with selected ion monitoring (SIM) to determine lidocaine, monoethylglycine-xylidide (MEGX), glycinexylidide (GX), and bupivacaine had high sensitivity peak levels of no more than 100 ng/mL. Other methods reported in the recent literature include capillary electrophoresis (CE), HPLC with a chiral stationary phase for enantiomeric separation, potentiometry using ion-selective electrodes, and fluorescence polarization immunoassay (FPIA). Sample preparation methods include microporous membrane liquid-liquid extraction and solid-phase extraction. Limits of detection (LOD) for the anesthetics and metabolites in plasma and urine for many methods are in the range 1 to 10 ng/mL.

Regulations

Local anesthetics are regulated by the Food and Drug Administration and Consumer Product Safety Commission (CPSC). The use and safety of the local anesthetics is reviewed and evaluated by the Center for Drug Evaluations and Research Anesthetic and Life Support Advisory Committee. In 1994, the CPSC voted unanimously to require child-resistant packaging for lidocaine formulations (containing >5% lidocaine) due to many cases of accidental ingestion by children resulting in 16 deaths. In 1993, the FDA's Anesthetic and Life Support Advisory Committee voted unanimously that evidence of carcinogenicity of the lidocaine metabolite 2,6-xylidine was insufficient for labels to mention that it caused tumors in laboratory rats. The FDA now requires that products that may metabolize to aniline compounds (lidocaine, prilocaine, and EMLA [the eutectic mixture of lidocaine and prilocaine) carry a warning of carcinogenic risk in the package inserts.

Metabolism

General Metabolism and Excretion

Metabolism of the amide local anesthetics is extensive in all species and is the primary factor limiting the length and intensity of anesthesia and governing elimination from the body. General pathways in metabolism include aromatic ring and side-chain hydroxylation, N-dealkylation, and hydrolysis of the amide bond. In primates (including man) and dogs, N-dealkylation appears to be the predominant pathway to metabolites detected in urine samples, with subsequent hydroxylation primarily in the 4-position of the xylidine moiety. In the rat and guinea pig, hydroxylation products, primarily in the 3-position of the xylidine moiety, are the predominant species excreted, with minor amounts of dealkylated products detected. Hydroxylation at the 4-position of 2,6-xylidine may predominate in all species, probably due to the lack of steric interference by the alkyl chain or pipecolyl ring (Dring, 1976).

Hydroxylation may occur primarily prior to amide hydrolysis, with minor amounts of metabolites being hydroxylated after hydrolysis. The local anesthetics along with their metabolites are predominantly excreted in the urine, with a small fraction excreted in the feces. Almost all of the hydroxylated metabolites are recovered in the urine as glucuronide or sulfate conjugates. Urinary excretion of unhydroxylated dealkylated metabolites (e.g., xylidine, pipecoloxylidide) is very low (~1-5%) after administration of the local anesthetics. The predominant metabolite excreted in the urine after lidocaine administration is 4-hydroxyxylidine (65-80% of the dose) and may be the predominant metabolite of the other amide local

anesthetics. Unfortunately, most studies have not been designed to detect the hydrolysis products containing the xylidine moiety.

In the liver, local anesthetics are metabolized by certain cytochrome isozymes. The metabolism of ropivacaine is mediated oxidatively by hepatic cytochrome P450 (CYP) 1A2 and 3A4 in humans and in rat hepatic cytochromes. Cytochromes CYP3A4 in humans and CYP2C11 and CYP2B1 in rats are responsible for the deethylation of lidocaine to MEGX *in vitro*. P450 isozymes 1A2 and 3A4 have been found to be involved in the metabolism of about 50% and 7%, respectively, of all prescribed drugs. The CYP1A2 enzyme is constitutively expressed in the liver and comprises about 10% of the total P450 in the liver. The CYP1A1 enzyme is only expressed after exposure to certain chemical inducers in human tissue. CYP3A4 comprises from 30% to 60% of the total liver P450s. It is possible that drug interactions may occur which decrease the metabolism of the local anesthetics. For example, 3-hydroxyropivacaine, the major *in vivo* metabolite of ropivacaine, is formed by CYP1A. If another drug is used concomitantly with ropivacaine and has a higher affinity for the CYP1A enzyme, then the half-life of elimination of the local anesthetic from the blood may be increased.

While there is large interindividual variation in metabolism within each study, examination of the means reveals a general pattern of metabolism within each species. There are very pronounced interspecies variations in the location of hydroxylation and amount of dealkylation of the amide local anesthetics. 3'-Hydroxylation on the xylidine moiety is predominant in rodents while 4'-hydroxylation predominates in primates. Biliary excretion of lidocaine is much more pronounced in rodents than it is in humans. One metabolite of lidocaine, 2-aminomethylbenzoic acid, has been found in rabbits, dogs, and possibly guinea pigs, but has not been detected in humans. The interspecies differences in the metabolism of lidocaine are best presented in Keenaghan and Boyes (1972).

Respired CO_2 is a route of elimination in mice but has not been adequately measured in humans. Respired CO_2 contained between 10.5 and 11.4% of the radiolabeled dose of mepivacaine when administered to mice.

The placental transfer of three metabolites of etidocaine was related to the lipophilicity of the metabolites. The greater the lipophilicity, the greater the cord/maternal plasma ratio.

Metabolism of drugs in the human neonate is less than in the human adult due to the immaturity of hepatic enzyme systems. This is also true in the case of the local anesthetics. The mean dose of mepivacaine excreted in the urine of human neonates unchanged is 43.4%, while only 3.5% is excreted in the urine of human adults unchanged. The mean percentage of lidocaine excreted unchanged in the urine of human neonates is 19.7%; however, 4.2% remains unchanged in the urine of adult humans.

Urinary excretion of the local anesthetics is pH-dependent. Acidic urine results in increased concentrations of the local anesthetics and some metabolites in the urine, whereas alkaline urine yields lower concentrations. For the most part urinary excretion of metabolites is pH independent.

Very little local anesthetic is eliminated in the feces of humans and only slightly more is eliminated in the urine of rodents. In rodents, it is thought that the metabolites excreted in bile are reabsorbed through the intestines to the bloodstream.

In the case of lidocaine and prilocaine, there is some evidence of *in vivo* and *in vitro* extrahepatic metabolism. Extrahepatic formation of MEGX after lidocaine hydrochloride injection was demonstrated in an anhepatic patient awaiting a liver transplant. It has been further

shown *in vitro* that extrahepatic metabolism in rats may occur in the kidney and lung, but not the brain. A very slow rate of MEGX and 3-hydroxylidocaine formation (0.022-0.024 nmol/min/mg protein) was observed in rat kidney microsomes as well as a slow rate of formation of MEGX (0.87 nmol/min/mg). The rate of formation of MEGX and 3-hydroxylidocaine by rat hepatic microsomes was 4.84 and 0.64 nmol/min/mg, respectively. There is evidence that CYP2B1 may be the sole isoenzyme responsible for the de-ethylation of lidocaine in rat pulmonary and renal microsomes. Extrahepatic clearance of prilocaine in humans is thought to occur because of its high hepatic extraction (2.85 L/min), which is higher than the hepatic blood flow rate in humans (~1.5 L/min).

Evidence for the Formation of Xylidine, *o*-Toluidine, and Other Metabolites

On the basis of structure, 2,6-xylidine could possibly be formed by the hydrolysis of the amide linkage in local anesthetics containing the xylidine moiety (all local anesthetics reviewed in this report except prilocaine). The hydrolysis of the amide linkage of prilocaine results in the formation of *o*-toluidine.

A review of the literature reveals that the major metabolites associated with the selected local anesthetics in this report are 4-hydroxyxylidine, hydroxylated parent compounds, and other hydroxylated dealkylated metabolites. The predominant metabolite excreted in the urine after lidocaine administration is 4-hydroxyxylidine (65-80% of the dose) and may be the predominant metabolite of the other amide local anesthetics containing the xylidine moiety. 2,6-Xylidine (XYL) should be considered a minor metabolite of the amide local anesthetics containing the xylidine moiety, except ropivacaine. No 2,6-xylidine was detected in human urine after administration of ropivacaine. *o*-Toluidine is a minor metabolite of prilocaine. Selected metabolites of the local anesthetics and their amounts in humans and rats are provided in the table following this metabolism summary. As can be seen in the table, there is still a large portion of the dose of the local anesthetics, other than lidocaine, that has not been accounted for.

Xylidine has been detected in the urine of humans after administration of etidocaine and in several species after administration of lidocaine. Concentrations of xylidine detected in 24-hour urine collections from human volunteers were 0.46% of the administered dose after etidocaine administration and 0.84-1.0% after lidocaine administration. The highest concentration of xylidine was detected in the urine of guinea pigs after lidocaine administration (16.2% of the administered dose). Only one study was located that sought to determine the concentration of xylidine in the urine of humans after administration of bupivacaine. No xylidine was found in the urine, but details of the study were not available.

Xylidine has been detected in the urine of neonates after the administration of anesthetics to the mother during delivery. After administration of etidocaine to seven mothers, xylidine (trace-1.9 □g in 5 neonates) and 4-hydroxyxylidine (2-6 □g in 3 neonates) were determined in 48-hour urine collections from the neonates. It was interesting that the neonates that produced xylidine had no detectable concentrations of 4-hydroxyxylidine and vice versa. Also, a set of twins was able to form one metabolite and not the other, which implicates genetic variables in neonatal metabolism.

Two metabolites, *N*-hydroxyxylidine from lidocaine and *o*-toluidine from prilocaine, have been shown to form hemoglobin adducts. Xylidine-hemoglobin adducts have been detected in the blood of tobacco smokers and nonsmokers after the proposed reaction of hemoglobin with *N*-hydroxyxylidine. In a study of nine patients undergoing treatment for cardiac arrhythmia,

concentrations of xylidine-hemoglobin adducts ranged from 110 to 690 ng 2,6-xylidine/g hemoglobin. Two patients had measurable xylidine-hemoglobin adducts prior to lidocaine infusion; one patient between 50 and 100 ng xylidine/g hemoglobin and the other had a concentration of 423 ng/g hemoglobin.

MEGX and GX are formed from the N-dealkylation of lidocaine. Concentrations of MEGX and GX determined in human urine samples range from 1.7-12.68% of the administered dose and 0.55-2.3% of the dose, respectively. Both MEGX and GX are hydroxylated on the xylidine ring after lidocaine administration to yield 3- and 4-hydroxymethylethylglycinexylidide, and 3- and 4-hydroxyglicinexylidide.

Pipecoloxylidide (PPX; pipecolylxylidide) is the N-dealkylated product of the amide local anesthetics that contain a pipecolyl moiety as the hydrophobic substituent attached to the amide intermediate—bupivacaine, mepivacaine, and ropivacaine. PPX does not appear to be a major metabolite of these anesthetics; however, it should be remembered that PPX is about twice as neurotoxic as bupivacaine. Excretion of PPX after administration of bupivacaine revealed that the two are differentially excreted in breast milk. While the mean bupivacaine serum and breast milk concentrations were highest two hours after epidural injection (0.23 and 0.09 μg/mL, respectively), the mean serum and breast milk PPX concentrations were highest 12 hours after administration (0.17 and 0.25 μg/mL, respectively).

The metabolites of the amide local anesthetics contain properties on their own that may affect the pharmacokinetics or toxicity of the local anesthetic. The *N*-hydroxyamine metabolite of lidocaine, *N*-hydroxylidocaine, and the dealkylated metabolite of prilocaine, *o*-toluidine, both form hemoglobin adducts resulting in hemoglobinemia after administration of each of the two local anesthetics. The lidocaine metabolites MEGX and GX have antiarrhythmic properties that may contribute to the antiarrhythmic activity of lidocaine. The antiarrhythmic properties of MEGX are approximately 80% of those of lidocaine. The hydantoin etidocaine metabolite 3-(2,6-dimethylphenyl)-5-ethyl-2,4-imidazolidininedione, which comprised 10% of the dose excreted in the urine, may contribute to the lower toxicity of etidocaine when compared to bupivacaine since hydantoins are known to have anticonvulsant properties.

Recommendations for Future Metabolism Studies

Lidocaine is the only amide local anesthetic for which most of the administered dose has been characterized. This was due to the fact that the Keenaghan and Boyes (1972) study of metabolism used lidocaine randomly tritiated in the benzene moiety. Less than 50% of the dose of the other amide local anesthetics (bupivacaine, etidocaine, mepivacaine, prilocaine, and ropivacaine) has been recovered in the urine. The characterization of the metabolism of these anesthetics is lacking due to the labeling of the anesthetics in the pipecolyl or carbonyl moiety, which does not account for xylidine or phenolic compounds. The design of future metabolite studies should allow for the accurate determination of the formation of xylidine and 4-hydroxyxylidine in urine, plasma, and other tissues after local anesthetic administration. More current tissue distribution studies to determine metabolite concentrations are also needed since there is evidence of extrahepatic metabolism in rat pulmonary, renal, and nasal microsomes *in vitro*. Also extrahepatic metabolism is supported by the clearance rates of the local anesthetics in human clinical studies, which are higher than hepatic clearance rates. Metabolism in the skin should be determined since lidocaine and prilocaine may persist in damaged skin for hours after application, and since there may be chronic dermal exposure to damaged skin from formulations

containing lidocaine. Many of the over-the-counter formulations are recommended for sunburns. It has been shown that lidocaine may inhibit the DNA repair of thymidine dimers in *Escherichia coli* after exposure to ultraviolet (UV) radiation. Since lidocaine has been found to be metabolized by rat nasal microsomes and nasal carcinomas have been detected in rats after exposure to the lidocaine metabolite 2,6-xylidine, the risk of applying lidocaine to the nasal cavity for the treatment of migraines should be assessed.

Careful attention should be devoted to sample work-up and analytical methods used to determine the concentration of metabolites. Standardization of sampling and analysis methods would be effective in establishing accurate information for the comparison of metabolism of the amide local anesthetics. Injection speed may be important for accurate separation of 3'- and 4'-hydroxylated metabolites. Both enzyme and acid hydrolysis should be employed to separate conjugated metabolites from unconjugated metabolites. Urinary excretion of metabolites of the amide local anesthetics may not accurately reflect the concentration of the metabolites in plasma. *In vitro* methods for the quantitative determination of metabolites do not accurately represent the actual *in vivo* urinary excretion of these metabolites due to the many physiological factors, especially hepatic blood flow and plasma protein binding, that affect the metabolism of the amide local anesthetics.

Pharmacokinetics

The potency and duration of action of the amide local anesthetics are closely related to the physical-chemical properties and structure of the individual anesthetic, respectively. The amide local anesthetics are weak bases that are variably lipophilic. The more highly substituted the alkyl or tertiary amines on or near the tertiary amine or in the aromatic ring, the more lipophilic the anesthetic. It is the lipophilicity, measured by the octanol/aqueous buffer partition coefficient that positively correlates with the anesthetic potency. Bupivacaine and etidocaine are the most potent and most lipophilic amide local anesthetics. The degree of interindividual variation in pharmacokinetic parameters seen in most studies is probably due to variations in factors that control clearance, such as blood flow, pH in blood and tissues, hepatic clearance rates, and possibly plasma protein concentrations. The amide local anesthetics in this report, except for ropivacaine are racemic mixtures containing both (R)- and (S)-enantiomers. The (S)-enantiomers of bupivacaine and prilocaine have been shown to have higher total body clearance and lower toxicity than the (R)-enantiomers in humans and dogs.

Absorption and distribution of amide local anesthetics varies depending on many factors, such as site and method of administration, blood flow characteristics, plasma protein binding, plasma pH, and the physical properties of the local anesthetic (i.e., pK_a, hydrophobicity, etc.). Absorption from the site of injection depends on the blood flow the higher the blood flow, the more rapid the rate at which plasma concentrations increase and the greater the peak plasma concentrations of the drug. When a local anesthetic is injected, the rate of absorption is greatest after intercostal block, followed by epidural, brachial plexus, and lower limb blocks, with subcutaneous (s.c.) infiltration being the slowest. If vasoconstrictors, such as epinephrine, are administered with the local anesthetic, then the rate of absorption into systemic circulation is reduced, usually allowing the safe dose of the anesthetic to be increased by 50-100%.

Subcutaneous and dermal application of the local anesthetics (prilocaine and lidocaine only) results in prolonged persistence of the local anesthetics at the site of application. Local anesthetics do not readily penetrate healthy human skin in their salt form; however, effects may

be seen if applied in their base form. Dermal absorption will be affected by the vehicle that contains the local anesthetic. The maximum anesthetic effect was observed one hour after application of lidocaine. The onset of anesthetic action after dermal application can be correlated with the local anesthetic's solubility in medium-chain triglycerides, which have properties similar to stratum corneum lipids. Dermal absorption of local anesthetics is affected by the vasculature of the area of application, age of the patient and condition of the skin. Lidocaine plasma concentrations after dermal application have been observed to peak 32 hours or longer after application in some individuals. In neonates, dermal absorption is more rapid than in adults due to the immaturity of the skin, which behaves more like a mucous membrane.

The absorption of the local anesthetics from the epidural space is biphasic, with an initial rapid phase followed by a slower terminal phase. Absorption from the epidural space into the blood is almost as rapid as absorption after dermal exposure. This may be due to the effect of the anesthetic on the local tissue vasculature. Bupivacaine and lidocaine have both been shown to produce vasodilation at the area of administration, thereby increasing the rate of absorption to the bloodstream from the site of administration. Another factor that may contribute to the slower absorption of the local anesthetics from the epidural space is its high fat content. The more lipid-soluble compounds, such as bupivacaine and ropivacaine, are released more slowly from the epidural space than the less lipid-soluble anesthetic lidocaine.

The transport of the amide local anesthetics across biological membranes is by passive diffusion, which in the case of the amide local anesthetics, is dependent on the pH. Higher concentrations of the anesthetic will be found in the tissue or compartment with lower pH. Decreasing the pH of the urine results in increased concentrations of the local anesthetic excreted in the urine. However, the excretion of metabolites in urine is not usually affected by pH.

The plasma protein binding of the amide local anesthetics by α_1-acid glycoprotein and albumin buffers the anesthetic dose from the tissues by sequestering it since mostly the unbound molecules are transported across biological membranes and into tissues. As much as 95% of the dose may be bound to plasma proteins in the case of bupivacaine and ropivacaine. Protein binding and pH play important factors in the transport of local anesthetics across the placenta. Acidosis of the fetus in mothers administered local anesthetics during delivery can result in higher fetal plasma and tissue concentrations of the local anesthetic. Even though plasma protein levels are lower in the fetus and the neonate, the greater volume of distribution and increased urinary excretion in the neonate maintain plasma concentrations similar to or close to concentrations seen in the mother.

The distribution of local anesthetics is characterized by a biphasic model, an α-phase and a β-phase. The α-phase is characterized by the rapid absorption of the anesthetic by the organs and tissue and is measured by the α-phase half-life ($T_{1/2\alpha}$). The $T_{1/2\alpha}$ of the amide local anesthetics is relatively rapid and is usually about 20 minutes or less. However, once the tissues become "saturated" with the maximum concentration of local anesthetic, then the elimination of the local anesthetic rapidly decreases until it approaches the $T_{1/2\alpha}$. The $T_{1/2\beta}$ is the total body clearance of the local anesthetic due to hepatic extraction and excretion. The $T_{1/2\beta}$ is under the influence of plasma protein binding of the local anesthetic, as well as hepatic clearance.

Local anesthetics are distributed throughout all body tissues, but the concentrations in each tissue will vary. The more highly perfused tissues, such as the lungs, heart, liver, and kidney, will have higher concentrations of the local anesthetic than less perfused organs. The lungs sequester large amounts of local anesthetics after administration so that plasma

concentrations of local anesthetic decrease considerably after passing through the lungs. The highest percentage of local anesthetic is found in the skeletal muscle, probably because it is the tissue that comprises the majority of human mass and not because there is a higher affinity for the local anesthetics in the skeletal muscle.

The placental transfer of the local anesthetics by passive diffusion is affected by the drug's molecular weight, lipid solubility, pK_a, protein binding, fetal pH, and fetal absorption. The amide local anesthetics readily cross the placenta by passive diffusion in the unbound un-ionized form. Studies have shown that the cord-to-maternal plasma concentrations of local anesthetics equilibrate quickly across the placenta and reach a relatively constant level 15-30 minutes after administration to the mother due to the high lipid solubility of the un-ionized form and their low molecular weight. The rate of transfer of a drug across the placenta is measured by the umbilical venous/maternal venous ratio (UV:MV) upon administration of the drug, and while fetal tissue saturation is incomplete, the umbilical artery/maternal venous (UA:MV) concentration ratio should increase to reach a plateau that approaches the UV:MV. During maternal drug absorption, a small gradient may exist if there is fetal metabolism. Both UV:MV and UA:MV are affected by transplacental pH and governed by the gradient of transplacental □-glycoprotein. The main cause of interindividual variation should be overcome by examining the UA:UV ratio, which gauges the extent of fetal equilibration and is not affected by □-glycoprotein concentration. The decreased amount of protein binding in the fetus and neonate would likely result in greater volume of distribution and may contribute to the reduced rate of elimination in the fetus. Elimination half-life of the local anesthetics in the human neonate is about 2-3 times longer than elimination in adults. The differences in UV:MV concentration ratios for the local anesthetics probably are due to the differences in protein binding; however, the concentration of *unbound* local anesthetic in the plasma of both mother and fetus should be the same at equilibrium.

Several factors may confound pharmacokinetics studies. Many human pharmacokinetics studies, especially the fetal transfer and obstetrics studies, allow supplemental dosing to achieve an effective level of pain management, which will vary greatly for each individual. This variability of the dose in human pharmacokinetics studies complicates dose interpretation. Also, many drugs that may effect the metabolism or pharmacokinetics of the amide local anesthetics, such as opioids, cemetidine, or propanalol, are routinely administered during medical treatment requiring local anesthesia. The interindividual variability in protein binding of the local anesthetics will effect the transfer across biological membranes, which may affect elimination rates and transfer across the placenta. Since most of the local anesthetic dose is contained in plasma, analyzing plasma will lead to higher concentrations than would be found in whole blood.

Summary of Selected Metabolites of Local Anesthetics and Their Amounts in Urine of Humans and Rats

Criteria	Local Anesthetic					
	Bupivacaine	**Etidocaine**	**Lidocaine**	**Mepivacaine**	**Prilocaine**	**Ropivacaine**
Percentage of Dose in Human Urine:						
Unchanged	0.13-6.0%	0.21%	2.1-4.76%	<5%		1.0%
2,6-Xylidine	n.f.[a]	0.46-2.16%	0.84-1.0%	-	X	-
Hydroxylated 2,6-xylidine	-	3.23-8.3	60.5-80.1%	-	X	-
o-Toluidine	X	X	X	X	0.75%	X
Hydroxylated *o*-toluidine	X	X	X	X	36.9%	X
MEGX	X	X	1.7-12.68%	X	X	X
GX	X	X	0.55-2.3%	X	X	X
PPX	1.21-5.0%	X	X	1.0-1.2%	X	2.8%
Hydroxylated parent compound	3.75-5.37%	~10.0%	0.2-1.58%	17.7-29.5%	-	37.3%
Other metabolites not mentioned above	4.9% and some not quantitated but considered to be minor	29.5%	36.38-36.68%	<10%	-	2.2%
Percentage of Dose in Urine of Rats:						
Unchanged	2.8-3.4%	n.a.	0.2%	-	-	n.a.
2,6-Xylidine	-	n.a.	1.5%	-	X	n.a.
Hydroxylated xylidine	X	n.a.	minute-12.4%	-	X	n.a.
o-Toluidine	X	n.a.	X	X	-	n.a.
MEGX	X	n.a.	0.7%	X	X	n.a.
GX	X	n.a.	2.1%	X	X	n.a.
PPX	0.3-1.1%	n.a.	X	X	X	n.a.
Hydroxylated parent compound	19.8-73.6%	n.a.	9.0-36.2%	50.0-59.2%	-	n.a.
Other metabolites not mentioned above	1.6-6.0%	n.a.	minute-36.9%	-	-	n.a.

An "X" in a column indicates that the compound is not a possible metabolite of that local anesthetic.
Dashes in a column indicates that the metabolite has not been detected in any studies.
n.a. = information not available because no studies were found
n.f. = not found in one study (Mather et al., 1971; Cited by Tucker and Mather, 1979) but study details were not provided.

Some Pharmacokinetic Parameters of the Amide Local Anesthetics

Local Anesthetic	RAP	PB (%)	$t_{1/2\alpha}$ (min)	$t_{1/2\beta}$ (hours)		UV/MV	V_{DSS} (L)	CL (L/min)	E_H (%)
				Adult	Neonate				
Bupivacaine	4	95	2.7	3.5	8.1	0.33-0.59	72	0.47-0.58	38
Etidocaine	2	94-95	2.2	2.6	6.42	0.23-0.55, 0.16-1.38[a]	133	1.11-1.22	74
Lidocaine	1	64-70	1.0	1.6, 1.8	3.05, 3.16	0.51	91	0.95	65
Mepivacaine	1	75-77	0.7	1.9, 3.17	8.95, 8.69		84	0.78	52
Prilocaine	1	40-55	0.5	1.5			261	2.84	
Ropivacaine	4	94		1.75			59	0.73	49

[a] This value is in whole-blood rather than plasma

Abbreviations: CL = rate of clearance from plasma; E_H = hepatic extraction; PB = Percent of local anesthetic bound to protein in plasma at 1 μg/mL serum, higher concentrations of the local anesthetic in plasma will decrease the percent bound to protein; RAP = relative anesthetic potency when compared to lidocaine; $t_{1/2\beta}$ = half-life of elimination from plasma; $t_{1/2\alpha}$ = half-life of absorption to tissue from plasma; UV/MV = umbilical venous/maternal venous plasma or serum concentration ratios; V_{DSS} = volume of distribution at steady state

Human Data

Systemic Effects

Local anesthetic drugs are potentially toxic if they are administered in high doses or into the wrong anatomic site, reaching the major target organs of toxicity, the brain and heart. The central nervous system (CNS) is more susceptible to the systemic actions of the drugs than the cardiovascular system (CVS) [which is also true in animals]. Therefore, CNS toxicity usually occurs before and is a good warning of CVS toxicity induced by local anesthetics. CNS toxicity ranges from excitation to convulsions. Symptoms and signs include feelings of lightheadedness, drowsiness, nervousness, irrational conversation, and tremors, and may be followed by seizures, respiratory arrest, myocardial depression, and even death. If the local anesthetic is rapidly administered by i.v. injection or given as a large dose, CNS depression immediately follows excitation, indicating that a dose-dependent and blood concentration-dependent action on the system may be exerted by the local anesthetic. The therapeutic blood-plasma/serum concentrations range from 0.25-5 μg/mL for bupivacaine, etidocaine, lidocaine, mepivacaine, prilocaine, and ropivacaine. The toxic levels range from 1-10 μg/mL. A comatose-fatal blood-plasma/serum concentration of 10 μg/mL was reported for lidocaine and ~20 μg/mL for prilocaine. The maximum tolerated doses for the above local anesthetics, excluding prilocaine, range from 1.4-9.8 mg/kg.

In regards to the CVS, local anesthetics can have a direct effect on both the heart and peripheral blood vessels. Although they have a suppressant effect on the heart, they can also act as vasodilators. Some local anesthetics, particularly the potent, highly lipid-soluble, highly protein-bound agents (e.g., bupivacaine and etidocaine) have induced sudden cardiovascular collapse, ventricular arrhythmias and fibrillation, and even death. The primary cardiac electrophysiologic effect is a lowering of the maximum rate of depolarization in Purkinje fibers and ventricular muscle. The drugs can also exert an effect on the mechanical activity of cardiac

muscle. At certain doses, they can serve as effective anticonvulsant agents and antiarrhythmic agents.

Clinically, local neurotoxicity can occur after an accidental subarachnoid injection of an epidural dose of a local anesthetic; up to 30 mL of anesthetic solution can be injected inadvertently into the subarachnoid space. Clinically used local anesthetics, however, rarely produce localized nerve damage. Intramuscular injection of the drugs has resulted in skeletal muscle changes. Bupivacaine and etidocaine were observed to cause more localized skeletal muscle damage versus lidocaine, mepivacaine, and prilocaine. The damage was reversible, with muscle regeneration complete within two weeks following injection.

Reproductive and Teratological Effects

Intracervical and intraspinal administration of bupivacaine to women have resulted in specific developmental abnormalities in the CVS and in behavioral and other postnatal effects on the newborn, respectively. Parenteral administration of lidocaine to pregnant women has shown specific developmental abnormalities in the CNS. In two male subjects given 1% lidocaine hydrochloride into the base of each cavernosum during a routine circumcision, impotence resulted.

The primary source of epidemiological data on potential teratogenic effects of local anesthetics is the Collaborative Perinatal Project. Bupivacaine, etidocaine, prilocaine, and pyrrocaine were not included and have not been adequately studied for teratogenic effects. There are no reports of congenital anomalies in children born to women who had these drugs administered during pregnancy.

Neonatal Effects

Acid-base status, Apgar scores, and neurobehavioral assessments have shown that local anesthetics have negligible effects on the neonate. However, significant behavioral differences (e.g., total looking times, preferences for visual stimuli) between infants (ranging in age from 20 hours to six days) exposed to local anesthetics during gestation and unexposed infants have been observed. Studies on whether epidural anesthesia adversely affects newborn behavior are conflicting.

Methemoglobinemia

Large doses of prilocaine have resulted in the development of methemoglobinemia; in general, at least a 600-mg dose is needed to produce clinically significant levels when administered epidurally in adults. Peak values of methemoglobin were reached six hours after administration of prilocaine but disappeared after 24 hours in most patients. The duration and intensity of cyanosis correlated with the duration and extent of methemoglobinemia. Lidocaine and xylidine intoxication has also produced methemoglobinemia. In contrast to prilocaine, single doses of lidocaine (500 mg) produced detectable amounts of methemoglobin but no cyanosis. Mepivacaine may induce methemoglobinemia as well as cyanosis.

Methemoglobin was detected in the blood of infants whose mothers were given epidural analgesia with prilocaine for delivery. Overall, direct application of EMLA (lidocaine-prilocaine cream) has not produced the condition. However, the combined use of EMLA (containing 12.5 mg prilocaine) and caudal anesthesia (5.4-6.7 mg/kg prilocaine) for herniotomy in premature infants resulted in toxic methemoglobinemia.

The Toxicity of Regional versus General Anesthesia

Regional anesthesia is preferred to general anesthesia during labor because of the fewer maternal deaths and serious injuries that occur. The toxic effects of regional anesthesia using amide local anesthetics on the fetus are primarily caused by maternal hypotension and seizures; effects of local anesthetics on the newborn infant are minimal and short-lived. General anesthesia results in brief, minimal depression of the healthy term neonate and greater occurrences of lower neonatal Apgar scores and respiratory depression.

Immunotoxicity

The few occurrences of allergic reactions (e.g., cutaneous lesions, edema, asthma, and anaphylactoid reactions) to amino amide local anesthetics have been linked with the presence of methylparaben, a preservative used in some commercial preparations of the agents and a compound that is chemically related to *p*-aminobenzoic acid and also a known allergen.

Lidocaine, in contrast to bupivacaine and mepivacaine, has been found to significantly inhibit natural killer (NK) cytotoxicity at low concentrations. In newborns delivered by elective cesarean section under epidural anesthesia (lidocaine hydrochloride with epinephrine), NK cell activity was significantly lowered compared to those delivered without labor by elective cesarean section under general anesthesia (thiopentone) but similar to those delivered vaginally with uncomplicated labor (no analgesia). Furthermore, in newborns born by cesarean section with epidural lidocaine anesthesia, neutrophil chemotaxis levels were significantly lowered compared to those of the other two groups; a significant inverse relationship between chemotaxis and lidocaine levels was observed.

Animal Data

Acute Toxicity

Lethal dose values for local anesthetics and their metabolites in several species via various routes (e.g., implantation, intraspinal, parenteral, and subcutaneous) have been reported. In rats, the oral LD_{50} value was 317 mg/kg with lidocaine. Using lidocaine hydrochloride monohydrate, the value was 292 mg/kg in mice. With mepivacaine, a value of >5000 mg/kg was obtained for both rats and mice. Oral LD_{50} values for metabolites were the following: >500 mg/kg with 4-hydroxy-2,6-xylidine in the rat; 234 mg/kg with MEGX in the mouse; 520 mg/kg in mice and 670 mg/kg in rats with *o*-toluidine; and 707 and 840 mg/kg, respectively, with 2,6-xylidine.

Only studies in mammals (laboratory rodents, rabbits, cats, dogs, monkeys, pigs, and sheep) were considered for inclusion. Endpoints studied included CNS and CVS toxicity (most commonly, ventricular arrhythmias and cardiovascular collapse), muscle degeneration and regeneration (particularly in rats), and maternal and fetal toxicity during delivery (mostly in sheep). Studies with bupivacaine comprised the largest amount of data. No effort was made to collect and summarize the lidocaine toxicity literature; the comprehensiveness of literature searches was complicated by the total numbers of lidocaine publications in the biomedical databases searched.

Short-term and Subchronic Exposure

In male rats, intrathecal implantation of 0.75% bupivacaine for up to eight days caused sensory anesthesia. When injected into the plantaris muscle of rats (0.15 mL of 0.5% w/v

bupivacaine hydrochloride in saline) daily for ten weeks, muscle degeneration and regeneration occurred. The mean weights of the muscle, the number of total branched fibers, and the maximum absolute twitch and tetanic tensions were increased compared to controls. When anesthetic-impregnated silastic cuffs containing 5-60% by weight bupivacaine were implanted into the soleus and/or lumbricalis muscles of rats and rabbits for three to 11 days, acetylcholine sensitivity was found in all muscle fibers. In pigs, epidural administration of bupivacaine (4 mL of 0.5% compound twice daily) for seven days caused slight inflammatory changes in ligamentum flavum and dura mater. In dogs, continuous intrathecal infusion (5.7-11.1 mg of 0.15-0.37% bupivacaine hydrochloride) for three to 16 weeks caused a markedly decreased response to toe-pinch of the hind limbs. Upon termination of bupivacaine infusions, all animals except one returned to fully normal gait.

Four potentially applicable lidocaine studies were not reviewed. No studies were available for the other amide local anesthetics.

Chronic Exposure

In rats, injection of bupivacaine (0.6 mL of 0.75% compound) into the right anterior tibial muscle daily for six months caused muscle fibers to be smaller than controls. Numerous internal nuclei, extensive fiber splitting, whorling of the intermyofibrillar network, and an enlarged zone of terminal innervation were also observed.

In newborn mdx mice and C57BL/10ScSn mice serving as controls, bupivacaine (0.1 mL of 0.5% compound) was injected into the right soleus muscle intermittently for up to nine or 12 months. At nine months, the muscle of the mdx mice had much variability in muscle fiber size; there was an increase in the percent small fibers compared with control mice. At nine and 12 months, the pattern of distribution of the fiber diameter for the right soleus muscle was more evenly distributed than the saline-injected left soleus muscle, while in control mice the pattern of distribution in the right soleus muscle did not differ from the left. In mdx mice, endomysial collagen content was higher than that of control mice.

Three potentially applicable lidocaine studies were not reviewed. No studies were available for the other amide local anesthetics.

Synergistic or Antagonist Effects

No synergism or antagonism has been observed in mixtures of either amide-amide or amide-ester local anesthetics. When added to solutions of local anesthetics, vasoconstrictors produce variable results, depending on the local anesthetic used and the type of anesthesia. In surface anesthesia, epinephrine and norepinephrine increased the action of local anesthetics at the superficial level. In lingual anesthesia, no effect was seen. In infiltration, conduction, spinal, and epidural anesthesia, vasoconstrictors increased the duration of anesthesia. In conduction and infiltration anesthesia, greater activity was observed with epinephrine versus norepinephrine.

The addition of glucose has inactivated some local anesthetics but not that of lidocaine. In the presence of carbon dioxide, the activity of solutions of lidocaine and mepivacaine was increased. Polymers have also increased the duration of action of local anesthetics. In the presence of the cholinergic substance pyridostigmine, the anesthetic effect of lidocaine was increased in surface anesthesia. The activity of the drug was also increased in surface, infiltration, and conduction anesthesia with the prior parenteral administration of the antidepressants imipramine and amitriptyline.

In dogs, i.v. lidocaine (0.01, 0.1, 1.0, and 10 mg/kg) worsened bronchoconstriction induced by histamine by reducing plasma catecholamine concentrations. In a cross-over study using human volunteers, pretreatment with erythromycin and itraconazole, inhibitors of CYP3A4, significantly increased peak plasma concentration of oral lidocaine (1 mg/kg). In rats, coinfusion of bupivacaine (2 mg/kg/min) with its desbutyl metabolite PPX resulted in a potentiation of the cardiac toxicity of the local anesthetic; there was a significant decrease in the doses causing arrhythmia and asystole. The decrease in the heart rate was greater than using either compound alone; two of six animals experienced cardiovascular collapse within five minutes.

Reproductive and Teratological Effects

When administered *in vitro* for 30 minutes to mouse oocytes, bupivacaine (0.01-100 μg/mL) caused fertilization and embryo developmental effects at the highest concentration.

In rhesus monkeys, no neonatal neurobehavioral effects of bupivacaine (epidural catheter infusion of 0.60 mg/kg of a 0.5% compound for 22 minutes) were observed. In cognitive testing, relatively low performance levels were attained in the bupivacaine infants. During the visual novelty preference test, they directed more, shorter fixations at visual stimuli. Furthermore, observation of behavior maturation patterns showed that the increase in manipulatory activity that normally occurs at two months of age was delayed in bupivacaine-exposed infants, while the increase in motor disturbance behaviors that normally occur at ten months of age was prolonged.

When pregnant rats were treated continuously with lidocaine doses equivalent to or up to five times the i.v. human dose, no teratogenic effects were observed in the offspring. However, when given as single injections in doses up to two times the hourly human dose, lidocaine resulted in neonatal behavioral changes in the offspring. In pregnant mice, single injections of lidocaine in doses 50 to 70% of the daily human infusion dose produced increased frequencies of CNS anomalies in the embryos. When treated with daily i.p. injections in doses equivalent to those used for regional block in women undergoing follicular aspiration immediately following fertilization, delayed embryonic development occurred. When given to baboons and sheep late in pregnancy, lidocaine (dose not provided) produced changes in perinatal adaptation.

In the offspring of pregnant rats and rabbits treated with up to two times the maximum recommended human dose, etidocaine produced no teratogenic effects. Prilocaine in doses up to three times the maximum human dose produced no adverse effects. In rats injected with the highest recommended mepivacaine human dose (6 mg/kg) on day 11 of pregnancy, significant abnormalities in behavioral test performance were observed in the offspring.

Carcinogenicity

No animal studies were available. In a U.S. case-control study, one of 361 brain tumor cases had an association with lidocaine.

Initiation/Promotion Studies

No studies were available.

Anticarcinogenicity Studies

No *in vivo* studies were identified. Several studies evaluated cytotoxicity and inhibitory effects *in vitro*, which are discussed below under "Other Data".

Genotoxicity

In the absence of metabolic activation (S9), lidocaine (dose not provided) was negative in the *Escherichia coli* DNA-polymerase-deficient assay system. In UV-irradiated cells of *E. coli*, lidocaine inhibited the excision-repair process. In *Salmonella typhimurium* strains TA98 and TA1900, lidocaine (8 mg/plate), in the presence and absence of S9, was not mutagenic. In intact murine L1210 cells, lidocaine (8 mM) produced no significant DNA damage compared to control cells; however, its addition to bleomycine (BLM) A_2-pretreated cells significantly increased DNA breakage by 4.4-fold.

No studies were identified for the other amide local anesthetics.

Cogenotoxicity

No studies were available.

Antigenotoxicity

No studies were available.

Immunotoxicity

No studies were available.

Other Studies

Cytotoxicity

In human M14 melanoma cells, treatment for two hours with bupivacaine hydrochloride (1.8 mM) reduced cell survival by 50%. A combination treatment with a temperature of 37 °C lowered ATP content by 86% but increased ADP and AMP content, and decreased the adenylated energy. Bupivacaine was found to also stimulate the basal rate of lactate production by 42%. When cells were exposed to 0.8 mM bupivacaine for up to 30 minutes, the cellular content of bupivacaine was greater at 42 °C than at 37 °C. Treatment of cells at 37 °C with 1.8 mM bupivacaine caused changes in the mitochondrial structure, the inner membrane, and the matrix, whereas cells heated at 42 °C for 50 minutes with 0.8 mM bupivacaine resembled untreated cells.

In mouse epidermal cells, lidocaine (1 mM) was an effective inhibitor of ornithine decarboxylase (ODC) induction by 12-*O*-tetradecanoylphorbol-13-acetate (TPA) and UV. Cells treated during and after TPA or after UV resulted in differential effects of 7% of TPA control and 18% of UV control.

In an epithelioid-type C3H mouse embryo cell line, lidocaine (1, 10, and 100 µg/mL) produced no multinucleation.

Addition of lidocaine (0.1-10 mM) to cultured murine L1210 cells incubated with BLM A_2 potentiated BLM A_2 cytotoxicity. A combination of 10 µM BLM A_2 and 8 mM lidocaine caused a 1000-fold increase in cell kill versus the use of the antitumor agent alone; with 30 µM BLM A_2, lidocaine increased cytotoxicity by more than 8000-fold. Furthermore, the local anesthetic (at 8 mM) reduced the total amount of cell-associated radioactivity compared to that seen with incubation of [^{3}H]BLM A_2 alone. Lidocaine (0.8 mM) also increased BLM A_2 cytotoxicity toward human head and neck squamous carcinoma cells.

When human osteoblastic Saos-2 cells were exposed for 48 hours to prilocaine (up to 10 mM), cell viability was decreased in a dose- and time-dependent manner. Co-incubation with

cycloheximide, however, increased the cell viability of the treated cells in a dose-dependent fashion; cell death was up to three times lower than that of the prilocaine-only treated cells.

Ropivacaine Effect on the Energy Metabolism of Ehrlich Ascites Tumor Cells

In Ehrlich ascites tumor cells, ropivacaine (up to 3.5 mM) inhibited the rate of oxygen consumption in the absence and presence of hydrophobic anion tetraphenylboron (TPB^-). Ropivacaine (2 mM) alone also partially reactivated oligomycin-inhibited respiration in the cells, but addition of TPB^- lowered the rate of oxygen uptake to a level close to that with oligomycin alone. In addition, low concentrations of ropivacaine were significantly effective in reducing oxygen consumption on uncoupled respiration of the cells.

Ropivacaine also improved total lactate production. In the absence of TPB^-, ropivacaine (up to 1 mM) produced no changes in the rate of production; the maximum was reached at 3 mM. In contrast, in the presence of TPB^-, ropivacaine immediately raised the rate; the maximum was reached at 2 mM.

Ropivacaine (dose not provided) was observed to also decrease the total adenine content by 50%. Depending on the concentration (not specified), ropivacaine decreased or collapsed mitochondrial membrane potential within the cells.

Porphyria

The following amide local anesthetics have been classified as unsafe for use in acute porphyria: etidocaine, lidocaine, mepivacaine, prilocaine, and pyrrocaine.

Structure-Activity Relationships

This section reviews the toxicity of several metabolites of the amide local anesthetics discussed in this report, including trimecaine (metabolite mesidine or 2,4,6-trimethylaniline). These are pipecolic acid, PPX, *o*-toluidine, and 2,6-xylidine.

Mesidine

Acute toxicity: In rats, an oral LD_{50} value of 660 mg/kg was reported for the hydrochloride form.

Subchronic exposure: In subchronic oral exposure studies, the compound resulted in growth inhibition and an increase in mean liver weights and kidney weights in both female and male rats, and an increase in the heart rate and testes mean weights of male rats only. Significant pathological changes in the liver and proliferation of bile ducts was also found. When injected as mesidine hydrochloride into the femoral vein of rats, methemoglobin formation was observed.

Carcinogenicity: In rats, mesidine produced heptaomas, cholangiocarcinomas, and severe cirrhosis of the liver.

Genotoxicity: In mice, mesidine produced DNA damage in liver cells as well as damage in bone marrow cells. It was mutagenic in *S. typhimurium* in the presence of metabolic activation and was positive for DNA repair in Chinese hamster hepatocytes.

Pipecolic Acid

Acute toxicity: In mice, an i.p. LD_{50} value of 610 mg/kg was reported. The mean convulsant activity was 0%.

Genotoxicity: Pipecolic acid was not mutagenic in *S. typhimurium* but was toxic to the bacteria at concentration >0.15 M.

PPX

Acute toxicity: In mice, an i.p. LD_{50} value of 140 mg/kg was calculated, and a mean convulsant activity of 100% was obtained with a concentration of 400 mg/kg. In rats, i.v. infusion of PPX produced seizure activity and asystole. The decrease in arterial blood pressure was greater than that from bupivacaine alone. In addition, plasma concentrations of PPX measured at 5 minutes were slightly higher than the bupivacaine concentrations. Coinfusion of PPX with bupivacaine produced a potentiation of the cardiac toxicity of the latter compound in rats.

o-Toluidine

Acute toxicity: In male Sprague-Dawley rats, an oral LD_{50} of 900 mg/kg body weight was calculated for undiluted *o*-toluidine. In mice, rats, and rabbits, the values were 515, 670, and 843 mg/kg body weight, respectively. An oral LD_{50} value of 2951 mg/kg was obtained for the hydrochloride form. In rabbits, *o*-toluidine was a mild irritant on the skin and a severe irritant on the eyes.

Short-term exposure: In rats, short-term studies with *o*-toluidine produced splenic congestion, increased hematopoiesis, hemosiderosis with bone marrow hyperplasia, epithelial changes in the bladder, methemoglobinemia, reticulocytosis, and anemia. Methemoglobinemia was also observed in mice, cats, and dogs.

In both mice and rats, *o*-toluidine hydrochloride in the diet caused a dose-dependent reduction in mean body weight gain, pigment deposition in the spleens of rats only, and renal and splenic pigmentation in mice.

Chronic exposure: Exposure to the hydrochloride resulted in reduced mean body weights in both animals. In rats, mortality was dose-related.

Reproductive and teratological effects: Topical application of *o*-toluidine to the skin of rats had paternal (e.g., spermatogenesis), maternal (e.g., changes or disorders in the menstrual cycle), and newborn effects (e.g., reduced weight gain).

Carcinogenicity: When fed to rats for 91 days, *o*-toluidine caused epithelial changes in the bladder. Given for two years in the diet, it produced hepatomas. In 83% of the rats, s.c. fibromas or fibrosarcomas were found. Subcutaneous injections of *o*-toluidine for over 397 days produced hyperplasia of the basal cells in the Zymbal glands.

When administered in the feed to mice, *o*-toluidine hydrochloride for 101 to 104 weeks produced several types of sarcomas of the spleen and other organs and hemangiosarcomas and hemangiomas of the abdominal viscera in both sexes. In males, mesotheliomas of the abdominal cavity or scrotum, an increased incidence of fibromas of the s.c. tissue, and hemangiosarcomas at

multiple sites occurred. In females, transitional-cell carcinomas of the urinary bladder, an increased incidence of fibroadenomas or adenomas of the mammary gland, and hepatocellular carcinomas or adenomas were observed.

In rabbits and guinea pigs, repeated s.c. injections of *o*-toluidine produced papillomas in the bladder. Injections in the hamster have resulted in no cancer.

Genotoxicity: Studies with *o*-toluidine have produced equivocal results. The overall conclusion regarding the mutagenicity of the compound was "nondefinitive" by the *Salmonella* Work Group for the U.S. EPA's Gene-Tox Program.

2,6-Xylidine

Acute toxicity: As 2,6-xylidine hydrochloride, an oral LD_{50} value of 2042 mg/kg was obtained in male Osborne-Mendel rats. In male Sprague-Dawley rats and CF_1 mice, the values were 1230 mg/kg and 710 mg/kg, respectively. As 2,6-xylidine, LD_{50} values for rats ranged between 630 and 1310 mg/kg. Administered as a single i.v. dose, 2,6-xylidine produced methemoglobinemia in cats but not dogs.

Short-term exposure: A study in dogs found decreased body weight, hyperbilirubinemia, hypoproteinmeia, and significant fatty degenerative changes in the liver. In rats, short-term exposure to 2,6-xylidine produced growth inhibition (weight retardation), red blood cell changes toward target cell anemia, pathological changes in the liver and kidney, slight chronic congestion in the spleens, pneumonia, ovarian cysts, distented uterine horns, an increase in microsomal glucuronyltransferase levels, and decreases in body weight and hemoglobin, erythrocyte, and hematocrit levels.

Chronic exposure: Studies in rats produced a reduction in body weight gain at a dose of 3000 ppm and in survival at levels of ≥1000 ppm.

Carcinogenicity: In studies with rats, 2,6,-xylidine in the feed produced papillary adenomas and carcinomas of the nasal cavity, as well as malignant mesenchymal tumors and rhabdomyosarcomas. Increased incidences of s.c. tissue fibromas and/or fibrosarcomas also occurred in both sexes, while neoplastic nodules of the liver were seen only in females.

Genotoxicity: The genotoxicity of 2,6-xylidine in *S. typhimurium* have been conflicting. In *E. coli* phage inhibition capacity was observed, and in hamster ovary cells cytogenic analysis and sister chromatid exchanges were seen. 2,6-Xylidine, however, failed to induce unscheduled DNA synthesis in rat hepatocytes, micronuclei in the bone marrow of mice, chromosome damage in polychromatic erythrocytes, and preferential killing of DNA repair-deficient bacteria in liver, lung, kidney, testes, and blood extracts from mice. Its ability to covalently bind to DNA ethmoid turbinates and liver of rats after oral pretreatment, however, indicated that 2,6-xylidine may be genotoxic under certain conditions.

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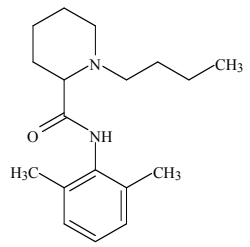
1.0 BASIS FOR NOMINATION

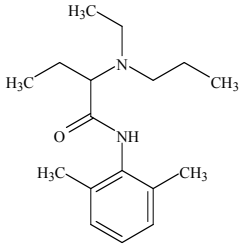
The nomination of dental local anesthetics by a private individual is based on their widespread use in dentistry, general medicine, surgery, and in some consumer products (e.g., topical skin preparations). The amide local anesthetics bupivacaine, etidocaine, lidocaine, and mepivacaine metabolize to 2,6-xylidine. Another amide local anesthetic that metabolizes to 2,6-xylidine is pyrrocaine, which is no longer used in the United States. The local anesthetic trimecaine, which would metabolize to the xylidine structural analogue mesidine (2,4,6-trimethylbenzeneamine), was also considered for inclusion in this report but was not due to its apparent lack of use in the United States. Prilocaine metabolizes to *o*-toluidine. Both 2,6-xylidine and *o*-toluidine have been shown to be carcinogenic in laboratory animals in NTP studies (Haseman et al., 1984; NTP, 1979, 1990). There are insufficient data on the mutagenicity and chronic toxicity of local anesthetics, including information on carcinogenicity. For this reason, the following report focuses on the amide local anesthetics available in the United States that metabolize to 2,6-xylidine and *o*-toluidine.

2.0 INTRODUCTION

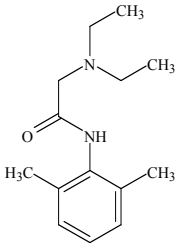
Figure 1. Structures of Local Anesthetics That Metabolize to 2,6-Xylidine or *o*-Toluidine



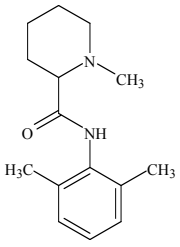
Bupivacaine



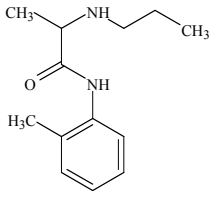
Etidocaine



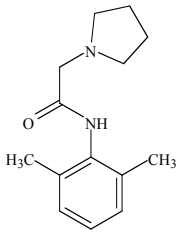
Lidocaine



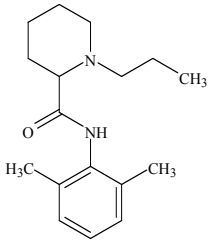
Mepivacaine



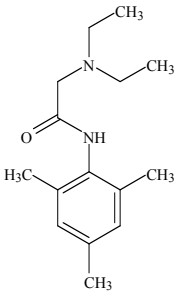
Prilocaine



Pyrrocaine



Ropivacaine



Trimecaine

2.1 Chemical Identification and Methods of Analysis

2.1.1 Chemical Identification

Compound	CASRN	Other Names/Synonyms
Bupivacaine	38396-39-3 (Replaced 2180-92-9)	1-Butyl-*N*-(2,6-dimethylphenyl)-2-piperidinecarboxamide; *dl*-1-Butyl-2',6'-pipecoloxylidide; 1-*n*-Butyl-2',6'-dimethyl-2-piperidinecarboxanilide; *dl*-*N*-*n*-Butylpipecolic acid 2,6-xylidide; 1-Butyl-2-(2,6-xylylcarbamoyl)piperidine; *dl*-1-*n*-Butylpiperidine-2-carboxylic acid 2,6-dimethylaniline; *dl*-Bupivacaine.
		Trade Names: Anekain (Pliva), Marcain (Winthrop)
hydrochloride	18010-40-7	**Trade Names:** Carbostesin* (Astra), Marcaine* (Winthrop)
hydrochloride monohydrate	14252-80-3	**Trade Names:** Marcain (BDH), Marcaina (Pierrel), Carbostesin (Woelm)
Etidocaine	36637-18-0	(±)-*N*-(2,6-Dimethylphenyl)-2-(ethylpropylamino)butanamide; 2-(Ethylpropylamino)-2',6'-butyroxylidide
hydrochloride	36637-19-1 (Replaced 52300-99-9)	**Trade Names:** Duranest* (Astra), Dur-Anest* (Astra)
Lidocaine	137-58-6	2-(Diethylamino)-*N*-(2,6-dimethylphenyl)acetamide; 2-Diethylamino-2',6'-acetoxylidide; □-Diethylamino-2,6-dimethylacetanilide; Lignocaine
		Trade Names: Cuivasil (IDC), Duncaine, Leostesin (Leo Pharmaceuticals), Lidothesin, Rucaina, Xylocaine (Astra Pharmaceuticals), Xylocitin, Xylotox
hydrochloride	73-78-9	
hydrochloride monohydrate	6108-05-0	**Trade Names:** Lidesthesin (Ritsert), Lignavet (C-Vet), Odontalg (Giovanardi), Sedagul (Wild), Xylocard (Astra), Xyloneural (Nicholas)
Mepivacaine	96-88-8	*N*-(2,6-Dimethylphenyl)-1-methyl-2-piperidinecarboxamide; 1-Methyl-2',6'-pipecoloxylidide; *dl*-*N*-Methylpipecolic acid 2,6-dimethylanilide; *dl*-*N*-Methylhexahydropicolinic acid 2,6-dimethylanilide
hydrochloride	1722-62-9	**Trade Names:** Carbocaina (Pierrel), Carbocaine hydrochloride (Winthrop), Chlorocain (Pharmaceutical Manufacturing), Meaverin (Woelm); Mepicaton (Pharmaton), Mepident (Parke Davis), Mepivastesin (Espe), Optocain (Bayer), Scandicain (Bofors); Polocaine* (Astra)
Prilocaine	721-50-6	*N*-(2-methylphenyl)-2-(propylamino)propanamide; □-Propylamino-2-methylpropionanilide; *N*-(□-Propylaminopropionyl)-*o*-toluidine; 2-Propylamino-*o*-propionotoluidide
hydrochloride	1786-81-8	**Trade Names:** Citanest (Astra Pharmaceuticals), Xylonest (Astra Pharmaceuticals); Propitocaine

Compound	CASRN	Other Names/Synonyms
Pyrrocaine	2210-77-7	*N*-(2,6-Dimethylphenyl)-1-pyrrolidineacetamide; 1-Pyrrolidineaceto-2',6'-xylidide; 2-(1-Pyrrolidinyl)-2',6'-acetoxylidide; 1-Pyrrolidinoaceto-2,6-dimethylanilide; EN-1010
		Trade Names: Endocaine (Endo), Dynacaine
hydrochloride	2210-64-2	
Ropivacaine	84057-95-4	(*S*)-*N*-(2,6-Dimethylphenyl)-1-propyl-2-piperidinecarboxamide; (*S*)-(-)-1-propyl-2,6-pipecoloxylidide; l-*N*-*n*-propylpipecolic acid-2',6'-xylidide
monohydrochloride	98717-15-8	
monohydrochloride monohydrate	132112-35-7	
Trimecaine	616-68-2	2-Diethylamino-2',4',6'-trimethylacetanilide; N-Sym-trimethylphenyldiethylaminoacetamide; 2-Diethylaminoacetyl-2',4',6'-trimethylanilide
hydrochloride	1027-14-1	**Trade Names:** Mesocaine, Mesidicaine, Mesokain

Sources: Budavari (1996) and *Rippel (1990)

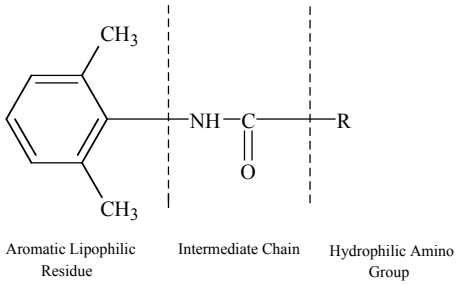
2.1.2 Analytical Determination

In the 1970s and 1980s, packed-column gas chromatography (GC) methods predominated for determining lidocaine and lidocaine metabolites monoethylglycinexylidide (MEGX) and glycinexylidide (GX) and bupivacaine, etidocaine, mepivicaine, and their common metabolite 2',6'-pipecoloxylidide (PPX). Detection methods included mass spectrometry (MS), flame ionization detectors (FID), and nitrogen (N)-FID. Sensitivities were at least 2.5 ng/mL, but were usually greater than 20 ng/mL. A few studies used capillary GC with detection by N-FID or MS with selected ion monitoring (SIM) to determine lidocaine, MEGX, GX, and bupivacaine with high sensitivity peak levels of no more than 100 ng/mL. A few high performance liquid chromatography (HPLC) studies used ultraviolet (UV) detection at 195-205 nm. Since the mid-1980s, capillary GC and HPLC methods have become more commonly used. Other methods reported in the recent literature include capillary electrophoresis (CE), HPLC with a chiral stationary phase for enantiomeric separation, potentiometry using ion-selective electrodes, and fluorescence polarization immunoassay (FPIA). Sample preparation methods include microporous membrane liquid-liquid extraction and solid-phase extraction. Plasma and urine LODs for many methods are generally in the range 1 to 10 ng/mL. Appendix J aims to identify the analytes, separation and detection methods, the matrix, and the limits of detection

(LOD) and quantitation (LOQ), when available, for each amide local anesthetic in biological matrices and pharmaceutical preparations.

2.2 Chemical Properties

In general, the amide local anesthetics in this report contain this general structure:



Compounds which usually exhibit local anesthetic activity have an aromatic and amine moeity, seperated by a lipophilic hydrocarbon chain and a polar group (Covino, 1986; Covino and Vasallo, 1976; all cited by Lenz et al., 1992). These molecular "divisions" are important in conveying certain physiological activities, such as solubility, time of onset of anesthesis, and degradability. Most local anesthetics are weak basic tertiary amines, which are comprised of three structural components: an aromatic moiety, and ester/amide linkage and an amine (McCarthy and Tuman, 1997). Aminoesters, such as tetracaine, have an ester linkage between the benzene ring and the intermediate chain that can be metabolized by ester hydrolysis primarily in the plasma by the enzyme pseudocholinesterase. However aminoamides, such as bupivacaine, etidocaine, lidocaine, mepivacaine, prilocaine, and ropivacaine, posses an amide linkage between the benzene ring and the intermediate amine group and are not metabolized by pseudocholinesterase.

Except for lidocaine, which contains no chiral bonds, and ropivacaine, which is only the *S*-isomer, these amide local anesthetics are a mixture of *R*- and *S*-enantiomers.

Table 1. Properties of Local Anesthetics That Metabolize to 2,6-Xylidine or *o*-Toluidine

Local Anesthetic	Properties							
	Molecular Formula	Molecular Weight	Physical State	Boiling Point (°C)	Melting Point (°C)	Solubility in Water	Lipid Solubility (25 °C)	pK_a (25 °C)
Bupivacaine	$C_{18}H_{28}N_2O$	288.43			107-108	Soluble	346	8.2
hydrochloride monohydrate	$C_{18}H_{28}N_2O \bullet HCl \bullet H_2O$	342.90			255-256	40 mg/mL		
Etidocaine	$C_{17}H_{28}N_2O$	276.42					800	8.1
hydrochloride	$C_{17}H_{28}N_2O \bullet HCl$	312.88			203-203.5	Soluble		
Lidocaine	$C_{14}H_{22}N_2O$	234.34	needles	$180\text{-}182_{4\ mm\ Hg}$, $159\text{-}160_{2\ mm\ Hg}$	68-69	Insoluble	43	8.2
hydrochloride	$C_{14}H_{22}N_2O \bullet HCl$	270.80			127-128			
hydrochloride monohydrate	$C_{14}H_{22}N_2O \bullet HCl \bullet H_2O$	288.81	crystals		77-78 (Crystals) 127-129 (Anhydrous)	Soluble		
Mepivacaine	$C_{15}H_{22}N_2O$	246.35	crystals		150-151		21	7.9
hydrochloride	$C_{15}H_{22}N_2O \bullet HCl$	282.80			262-264	Soluble		
Prilocaine	$C_{13}H_{20}N_2O$	220.31	white needles, odorless	$159\text{-}162_{0.1\ mm\ Hg}$	37-38		25	8.0
hydrochloride	$C_{13}H_{20}N_2O \bullet HCl$	256.77	white crystals		167-168	Soluble		
Pyrrocaine	$C_{14}H_{20}N_2O$	232.33	crystals		83			
hydrochloride	$C_{14}H_{20}N_2O \bullet HCl$	256.77	crystals		205	Soluble		
Ropivacaine	$C_{17}H_{26}N_2O$	274.41	crystals		144-146		115	8.2
Monohydrochloride	$C_{17}H_{26}N_2O \bullet HCl$	310.87	crystals		260-262	Soluble		
Monohydrochloride Monohydrate	$C_{17}H_{26}N_2O \bullet HCl \bullet H_2O$	328.88	crystals		269.5-270.6			
Trimecaine	$C_{15}H_{24}N_2O$	248.37	crystals	$187_{6\ mm\ Hg}$; $154\text{-}155_{0.6\ mm\ Hg}$	44			
hydrochloride	$C_{15}H_{24}N_2O \bullet HCl$	284.83	crystals		140			

Source: Budavari (1996). Lipid solubility and pK_a values taken from Feldman (1994).

2.3 Commercial Availability

The companies that supply these local anesthetics as well as the packaging amounts are contained in the table below.

Table 2. U.S. Suppliers of Local Anesthetics During 1998

Corporation	Location	Supplies	Bulk Supplier	High Purity Supplier	Bulk and High Purity Supplier
Aceto Corporation	Lake Success, NY	BUP1, BUP2	LID1, LID3, MEP2,		
Accurate Chemical and Scientific Corp.	Westbury, NY	LID1			
Acros Organics	Pittsburgh, PA	LID1			
Alfa Chemicals	Kings Point, NY	BUP2, LID3			
American Radiolabeled Chemicals	Saint Louis, MO	LID4			
Atomergic Chemetals Corporation	Farmingdale, NY		BUP1, LID1, LID3, MEP1		
Ceres Chemical Company	White Plains, NY				BUP2, MEP2, PRI1
ICN Biomedicals, Inc.	Costa Mesa, CA	LID1, PRI1			
Integra Chemical Company	Renton, WA	LID1, LID3			
Interchem Corporation	Paramus, NJ		LID1, LID3		
Monomer-Polymer & Dajac Laboratories, Inc.	Feasterville, PA	LID1, LID3			
Napp, Inc.	Saddle Brook, NJ		BUP1, ETI, LID1, LID3, PRI1, PRI2		
Pfaltz & Bauer, Inc.	Waterbury, CT	LID1, LID3			
Reasearch Biochemicals International	Natick, MA			LID2, LID3	
Ruger Chemical Company	Hillside, NJ		LID1		
Salor (A Division of Aldrich Chemical Co.)	Milwaukee, WI		LID1		
Sigma Chemical Company	Saint Louis, MO	BUP3, LID1, LID2, LID5, PRI2			
Spectrum Quality Products, Inc.	Gardena, CA	BUP3, MEP2, PRI2	LID1, LID5		
Triple Crown America, Inc.	Perkasie, PA				BUP1, LID1, MEP1
TCI America, Inc.	Portland, OR	LID1			
Wacker Silicones Corporation	Adrian, MO			LID1	
Wyckoff Chemical Company	South Haven, MI				LID1

Sources: ChemSources USA, 1999, and American Chemical Society, 1999.

BUP1 = Bupivacaine
BUP2 = Bupivacaine hydrochloride
BUP3 = Bupivacaine hydrochloride, monohydrate
ETI = Etidocaine
LID1 = Lidocaine
LID2 = Lidocaine *N*-ethyl bromide, quaternary salt
LID3 = Lidocaine hydrochloride
LID4 = Lidocaine hydrochloride (Carbonyl-$_{14}$C)
LID5 = Lidocaine hydrochloride monohydrate
MEP1 = Mepivacine
MEP2 = Mepivacine hydrochloride
PRI1 = Prilocaine
PRI2 = Prilocaine hydrochloride

3.0 PRODUCTION PROCESSES

Bupivacaine hydrochloride is produced by the reaction of 2,6-xylidine and piperidine-2-carboxylic acid chloride hydrochloride. The product, pipecoloxylidide (PPX), is then alkylated with 1-butylbromide to form bupivacaine hydrochloride (Rippel, 1990).

Mepivacaine is prepared by treating 2,6-xylidine magnesium bromide with ethyl-1-methyl-2-piperidinecarboxylate. It can also be prepared by hydrogenation and then N-methylation of pipecolic acid 2,6-xylidide (PPX) (Rippel, 1990).

Etidocaine is synthesized by acylating 2,6-xylidine with 2-bromobutyric acid. The bromine atom in the resulting compound is then replaced with iodine by boiling with potassium iodide in methanol. Treating the reaction mixture with *n*-propylamine gives an *n*-propylamino compound, which is finally alkylated with diethyl sulfate (Rippel, 1990).

Lidocaine hydrochloride is prepared by the reaction of 2,6-xylidine and chloroacetyl chloride in glacial acetic acid with the addition of sodium acetate. The resulting product, chloroacetyl-2,6-dimethylanilide, is then boiled with diethylamine in a solvent such as benzene. Crystallization of the hydrochloride occurs with one molecule of water, which can be removed by drying (Rippel, 1990). It is produced by Wycoff Chemical Company, located in South Haven, Michigan (SRI, 1999).

Prilocaine is the result of treating 2-aminotoluene with 2-bromopropionyl chloride and then *n*-propylamine (Rippel, 1990).

In patents awarded to Astra Laekemeded AB of Sweden, ropivacaine was produced by the amidation of (*L*)-pipecolic acid chloride hydrochloride by 2,6-xylidine. The (*L*)-pipecolic acid precursor was prepared by resolution of racemic pipecolic acid with (+)-tartaric acid (Ekenstam and Bovine, 19987; Ekenstam et al., 1985).

4.0 PRODUCTION AND IMPORT VOLUMES

Production statistics for the local anesthetics were only available from 1980 to 1984. In 1980, production of all local anesthetics was 61.5 short tons and lidocaine production comprised 41% of the total (36.5 tons) (USITC, 1981). In 1982, production of all local anesthetics was 53 short tons and lidocaine production comprised 28% of the total (30 tons) (USITC, 1983). In 1984, production of all local anesthetics was 77 short tons and lidocaine production was not reported (USITC, 1985). This is the reported production of bulk medicinal chemicals only.

5.0 USES

Local anesthetics are used to produce anesthesia by blocking the conduction of nerve impulses in sensory and motor nerve fibers (Lenz et al., 1992). Local anesthetics may be used in either human or veterinary medicine. All of the local anesthetics mentioned in this report are used in human medicine. In veterinary medicine, mepivacine and bupivacaine can be used, but lidocaine is preferred because of its chemical stability, sedative effects, lack of tissue damage, low hypersensitivity, and antiarrhythmic effect (Muir and Hubbell, 1989).

In human medicine, local anesthetics may be used in local infiltration, peripheral nerve blocks, intravenous (i.v.) regional blocks, central neural blockade, or topical anesthesia. Local anesthetics used in local infiltration are injected subcutaneously or intradermally in the region where the anesthetic effect is needed (Strichartz and Berde, 1994). As a peripheral nerve block, local anesthetics are applied regionally to inhibit nerve impulses in the peripheral nervous system. Minor nerve blocks involve the nerve blockade of one nerve entity, such as the ulnar or radial nerve. Major blocks may involve the blocking of two or more distinct nerves or nerve plexus. Peripheral nerve blocks are used for post-operative surgery and brachial plexus block (e.g., upper limb surgery). Central neural blocks may be either spinal or epidural.

Local anesthetics have become increasing utilized in the blockade of pain during normal and cesarean deliveries in pregnant women. In 1992, as many as 29% of women used epidural anesthesia for the relief of pain during hospital deliveries in the United States, a 100% increase over use in 1981 (Hawkins, 1994; Cited by King, 1997). In a survey of 750 hospitals in the United States from 1981 to 1997, the number of women requesting epidural or spinal injections of local anesthetics during obstetric procedures tripled at large hospitals (from 22 to 66%), and from 1992 to 1997, the number doubled at smaller hospitals (from 21 to 42%) (Grady, 1999). At St. Lukes-Roosevelt Hospital Center in New York City, one physician reported the use of epidural regional anesthesia among all women giving birth at the hospital increased from around 10% in 1989 to about 90% in 1999.

The choice of which local anesthetic to use is determined by the type and duration of treatment to be applied. Bupivacaine is used in extradural obstetric procedures and in post-operative analgesia because it has very little effect on motor blockade, allowing necessary muscles to be used during the delivery. Currently, bupivacaine is the most widely used drug for epidural anesthesia (Gustorff et al., 1999); however, the use of ropivacaine for epidural

anesthesia is increasing since studies have shown that it is as effective as bupivacaine, but ropivacaine results in less motor block and less systemic toxicity (Knudsen et al., 1997; Brockway et al., 1991; both cited by Gustorff et al., 1999). Etidocaine, on the other hand, posseses a very rapid onset of action. It too has a long duration of action; however, etidocaine results in profound motor blockade. This drug is used only when motor sensory (nerves that control movement) should be suppressed (i.e., surgery on limbs).

Lidocaine (given epidurally) is the preferred anesthetic for the relief of post-operative pain in children (Kakiuchi et al., 1999). Lidocaine is also used topically for the management of post-operative peripheral pain as a result of surgery (Kokinsky et al., 1999). Lidocaine is used for the management of pain due to severe burns due to its analgesic and anti-inflammatory effectsPal et al., 1997). The use of lidocaine in burn treatment is controversial due to toxic reactions (allergic reactions and decreased epithelialization) which have developed during treatment, but have not been proven to be caused by lidocaine (Pal et al., 1997). It is usually applied as an aerosol to the site of the wound after such procedures as circumcision and tonsillectomy. Topical aerosol lidocaine (10%) is used in adults for post-operative relief of peripheral pain after herniorraphy and hysterectomy (Kokinsky et al., 1999).

Topical anesthetics may be used for the management of pain due to hemorrhoids, toothaches, or skin ailments. However, lidocaine is the only local amide anesthetic in this report that is sold in over-the-counter preparations (2.5-5.0% lidocaine) in the United States for the relief of burns and irritation of the skin.

Lidocaine (2.5%) is combined with prilocaine (2.5%) in the EMLA prescription formulation cream, which is used to soothe painful skin conditions such as shingles (Varicella Zoster) (Auwaerter, 1998). EMLA is also used on donor sites for cutting of split skin grafts, for pain-free venepuncture, pain relief from molluscum contagiosum in children, and removal of genital warts and other superficial surgical procedures (Juhlin et al., 1989). EMLA is the topical anesthetic of choice for male circumcision (Brown et al., 1999). EMLA is not recommended for use in infants younger than six months of age in Canada and is only licensed for use in infants older than one month in the United States (Gazarian et al., 1995).

Besides being used as a topical anesthetic, lidocaine also is used as an antiarrhythmic agent; however, it should be administered parenterally due to its short half-life (von Philipsborn et al., 1985). The quantification of the formation of the lidocaine metabolite (MEGX) following

i.v. administration of lidocaine (usually 1 mg/kg) has been proposed to evaluate liver function of cirrhotic patients, but there are still some questions concerning the validity of this application (Schinella et al., 1993; Munoz et al., 1999; Balistreri et al., 1992; Oellerich et al., 1990; Reichen, 1993).

Lidocaine has also been approved for use as an intranasal spray for the treatment of migraine (Deshpande et al., 1999). The nasal delivery of lidocaine is of importance since the metabolite of lidocaine, 2,6-xylidine, has been linked to the formation of nasal carcinomas in rats and nasal microsomes of rats have been shown to metabolize lidocaine *in vitro* (Koujitani et al., 1999). Lidocaine was also found to be effective in the reduction of sensitivity of upper airway reflexes associatied with the classic symptomas of upper espiratory tract infection (common cold) (Hall et al., 1999). A new dental anesthetic delivery sytem, Dentipatch®, contains a fiber patch impregnated with lidocaine. When the patch is applied to the gums, lidocaine is realeased. In children, bupivacaine and lidocaine are most frequently used for brachial plexus blocks and major neuraxial blocks (intra- and post-operative pain management) (Brown et al., 1999). Bupivacaine is used in pediatric thoracic and abdominal procedures as well as lower limb blocks.

Local anesthetic bases have poor solubility in water, but are generally soluble in organic solvents due to their hydrophobicity (Strichartz and Berde, 1994). Because of this, local anesthetics are usually marketed as water-soluble hydrochloride salts.

Local anesthetic formulations may also contain the vasoconstrictor epinephrine (adrenaline) to shorten the induction time and increase the duration and intensity of the nerve blockade (Bonica et al., 1980; cited by Schierup et al., 1988). The risk of toxicity is reduced when epinephrine is used because drug absorption is retarded due to slow release from the area of administration. This is especially true when local anesthetics are used for local infiltration, with lidocaine having the most prolonged duration (Strichartz and Berde, 1994).

In 1990, U.S. sales of the injectable local anesthetics Xylocaine® (lidocaine hydrochloride) and Marcaine® (bupivacaine hydrochloride) were 22.5 million and 10.7 million dollars, respectively (Lenz et al., 1992).

Pyrrocaine, developed in 1960, was used mainly as an infiltration and nerve block dental anesthetic (2.0% solution) in the 1960s and favored due to its rapid onset; however, there is no evidence that it is currently used commercially (Zsigmond and Patterson, 1969).

Table 3 describes the use of local anesthetics in human, as well as veterinary, medicine.

Table 3. Uses of Local Anesthetics

Local Anesthetic	Introduction	Use	Concentration (%)	Form	Area of Use	Trade-Names
In Human Medicine:						
Bupivacaine	1963	Peripheral Nerve Blocks	0.25-0.75	Solution	Lumbar epidural	
		Epidural	0.25-0.75	Solution	Lumbar epidural	
		Infiltration, Parenteral	0.25-0.5	Solution	Area to be anesthetized	Marcaine, Sensorcaine
		Spinal Anesthesia	0.5-0.75	Solution	General	
Etidocaine	1972	Infiltration, Parenteral	0.5-1.0	Solution	Area to be anesthetized	Duranest-MPF
		Peripheral Nerve Blocks	1.0-1.5	Solution	Lumbar epidural	
		Epidural	1.0-1.5	Solution	Lumbar epidural	
Lidocaine	1948	Topical-General	2.0-10.0	Solution	Tracheobronchial tree, nose	Xylocaine
			2.0	Jelly	Urethra	Xylocaine
			10.0	Suppositories	Rectum	Xylocaine
		Topical-Dental	2.0-4.0	Solution	Oropharynx	Zilactin-L, Xylocaine
			2.0	Viscous	Oropharynx	Xylocaine Viscous
			10.0	Aerosol	Gingivival mucosa, Post-operative wound pain	Xylocain
			4.6	Dermal Patch	Gingivival mucosa	DentiPatch
		Infiltration, Parenteral	0.5-1.0	Solution	Area to be anesthetized	Xylocaine, Nervocaine, Lidoject, Dilocaine, Dalcaine, Duranest
		Regional Intravenous	0.25-0.5	Solution	Area to be anesthetized	
		Peripheral Nerve Blocks	1.0-2.0	Solution	Lumbar epidural	
		Spinal Anesthesia	1.5, 5.0	Solution	General	
		Anirrythmic			Inravenous	
		Migraine Headaches	4.0	Solution	Nasal Spray	

Table 3. Uses of Local Anesthetics (Continued)

Local Anesthetic	Introduction	Use	Concentration (%)	Form	Area of Use	Trade-Names
Mepivacaine	1957	Infiltration, Parenteral	0.5-1.0	Solution	Area to be anesthetized	Carbocaine, Isocaine, Polocaine
		Peripheral Nerve Blocks				
		Epidural	0.25-0.5	Solution	Lumbar epidural	
		Spinal Anesthesia	0.5-0.75	Solution	General	
Prilociane	1960	Topical				
		Infiltration, Parenteral	0.5-1.0	Solution	Area to be anesthetized	Citanest Forte, Citanest Plain
Pyrrocaine	1960					
Ropivacaine	1996	Peripheral Nerve Blocks	0.25-0.5			
		Epidural	0.25-0.5	Solution	Lumbar epidural	
		Infiltration, Parenteral	0.5-1.0	Solution	Area to be anesthetized	
In Veterinary Medicine:						
Bupivacaine		Topical	0.25	Cream, Solution, Aerosol		
		Infiltration	0.25-0.5			
		Intraperitoneal, Interpleural	0.25-0.5			
		Epidural, Spinal	0.25-0.5			
Lidocaine		Topical				
		Epidural, Spinal	2.0			
Mepivacaine		Topical				

Human use data taken from Strichartz and Berde (1994); veterinary use information taken from Pascoe (1997).

6.0 ENVIRONMENTAL OCCURRENCE AND PERSISTENCE

Environmental exposure may occur during manufacture and production or by disposal of products containing local anesthetics. No information was located concerning the fate of local anesthetics in the environment, but environmental exposure to local anesthetics is expected to be minimal.

7.0 HUMAN EXPOSURE

Human exposure occurs by the topical application or injection of a local anesthetic or combination of local anesthetics during medical treatment. Oral ingestion may also occur if a local anesthetic is applied topically to the oropharynx area. The amount and duration of exposure depend on the type of anesthetic used and the method of administration. The doses of local anesthetics, duration of application, and the duration of effect are given in **Table 4**.

Topical application of lidocaine and EMLA cream (2.5% lidocaine, 2.5% prilocaine) may result in chronic exposure in order to manage pain from chronic or reoccurring conditions, such as skin wheels, sunburn, or shingles; whereas, other administration methods of local anesthesia result in only acute exposure. Lidocaine is available in several over-the-counter (OTC) formulations sold in stores and over the Internet (e.g., Afterburn® Aloe Gel [0.5% lidocaine, Tender Corp.]; Bactine® liquid [2.5% lidocaine, Bayer Corp.]; and Solarcaine® Aloe Gel [0.5% lidocaine, Schering-Plough]. These OTC formulations are generally used for the temporary relief of painful skin conditions, such as sunburn, windburn, minor burns, chapped, or irritated skin, which would result in acute or subchronic exposure. The OTC preparations contain no more than 2.5% lidocaine weight per volume (w/v) and can be applied three to four times a day in adults (InteliHealth–Home to Johns Hopkins Health Information, 1994). The prescription formulations usually contain 5.0% lidocaine w/v. Chronic exposure to lidocaine may occur when used to treat the pain associated with shingles (herpes zoster). Shingles, a second outbreak of the virus that causes chickenpox, will occur in approximately 1 in 5 adults over the age of 50 (Mayo Clinic, 1997). The latent virus causes postherpetic neuralgia - a painful skin condition caused by damage to nerve fibers that can continue after the rash and blisters of shingles have subsided. Half of the people over 60, and 75% of the people over 70 who develop shingles will also develop postherpetic neuralgia (Mayo Clinic, 1997). The pain from postherpetic neuralgia may persist for months or even years after the episode of shingles. There is evidence that

lidocaine may remain at the dermal site of application for an extended time, with peak concentrations occuring as long as 24 hours after a single topical applicationof a 5.0% lidocaine formulation (Dal Bo et al, 1999). However, blood absorption from mucous membranes (i.e., gigiva, nasal passages) is much more rapid and would not lead to a great accumulation of lidocaine at the site of administration (Noven Pharmaceuticals, 1997). It is difficult to determine the extent of exposure of humans to chronic applications of topical anesthetics since no studies were found that determined the plasma levels of lidocaine after repeated topical administration.

Chronic exposure may also occur as a result of lidocaine use for extensive or repetitious dental procedures. For example, a full mouth reconstruction could require the injection of 5-8 cc of 2% lidocaine (10-16 mg) per weekly or biweekly session for up to six months (Nickel, 1996).

The dose of intravenous, infiltration, epidural or spinal injections of local anesthetics may vary depending on the local anesthetic, amount of analgesia desired, location of administration, desired time of onset and duration of anesthetic effect. There is evidence from the studies reviewed that bupivacaine and ropivacaine are the only local anesthetics which may result in the longest exposure periods as a result of epidural infusion for post-operative pain or for the management of pain during certain medical procedures. The use of epidural anesthesia for post-operative pain management resulted in an infusion period of 72 hours (Scott et al., 1997). Epidural infusion of bupivacaine and ropivacaine, seperately for two periods (each lasting three days and seperated by a one week interval), were used during brachytherapy in a 21 month old girl (Gustorff et al., 1999).

Many new application methods for transdermal and intradermal administration of the amide local anesthetics have been approved for use in the United States. A commercially available device for the controlled release (electrotransport or iontophoresis) of lidocaine transdermally is currently being marketed under the name Phoresor (Edgren et al., 1993). A method of pediatric iontophoresis is currently marketed as Numby Stuff® (Iomed®) and is used with a special formulation of lidocaine (Iontocaine®) to reduse the pain associated with needle sticks in children (PSL Group, 1999). A patch marketed under the tradename DentiPatch® is also available for the transdermal delivery of lidocaine via the gingiva (Noven Pharmaceuticals, 1999). Another patch, Lidoderm® (Endo Pharmaceuticals), was the first patch approved for relief of pain specifically associated with shingles; however, it is only approved for 12 hour use in a 24 hour period to avoid toxic doses (Saper, 1999). One study touted the advantages of using

a jet injection route for intradermal application of lidocaine for the management of pain during i.v. catheterization (Zsigmond et al., 1999). Lidocaine has also been approved for use as an intranasal spray for the treatment of migraine (Deshpande et al., 1999).

Because of the current widespread use of local anesthetics, mainly bupivacaine and mepivacaine, in pregnant mothers to relieve pain during delivery, it is becoming more important to assess the exposure of the neonate to local anesthetics and the potential risk. In a study of merconium extracted from randomly chosen neonates, 33.7% had been exposed to lidocaine, 18.4% has been exposed to mepivacaine, and 3.1% were exposed to bupivacaine (Ostrea et al., 1998 and Ostrea et al.,1999).

The dose and concentration of local anesthetics used during delivery has decreased in the past few years due to the need for less motor blockade during anesthesia (King, 1997). This has been achieved by the addition of lipid-soluble opioid drugs that potentiate the anesthetic effect, such as morphine or fentanyl, to the anesthetic regime during delivery. Today the combination used most often is spinal, epidural or spinal-epidural adminstration with bupivacaine (0.125%) and either fentanyl, sufentanil or meperidine (King, 1997; James, 1997).

Neonates may be exposed to topical EMLA or lidocaine, commonly used today for needle sticks and male circumcision (Woodman, 1999). In 1984, 76.4% of male babies born in the United States were circumcised; however, a majority of doctors do not use local anesthetics during circumcision (Davenport and Romberg, 1984; Wellington and Ryder, 1993); cited by Woodman, 1999). Information on blood concentrations in the neonate after topical administration of EMLA and lidocaine may be found in **Section 9.1.2**.

Treament of cardiac arrhythmia results in high doses of lidocaine than are normally used in other treatments. The usual dose of lidocaine used for local anesthesia is 1 mg/kg; however, when lidocaine is used for cardiac arrhythmias the dose can be as high as 50 mg/kg (Bryant et al., 1994).

Table 4. Human Therapeutic Dose and Exposure Levels for Local Anesthetics

Anesthetic and Intended Use	Concentration (%)	Usual Dose (mg)	Maximum Dose (mg) *	Duration of Anesthetic Effect (hours) *
Bupivacaine				
Infiltration	0.25-0.5		175 (225)	0.25-0.5 (0.5-1.5)
Minor Nerve Block	0.25	12.5-50		3.0-6.0 (4.0-8.0)
Major Nerve Block	0.25-5.0		225	6.0-12.0
Epidural	0.25-0.75	37.5-225		3.0-5.0
Spinal	0.5-0.75	15-22.5		1.25-2.5
Etidocaine				
Infiltration	0.5-1.0		300 (400)	2.0-2.5 (2.5-7.0)
Minor Nerve Blocks	0.5	25-100		2.0-4.0 (3.0-7.0)
Major Nerve Blocks	0.5-1.0		400	6.0-12.0
Epidural	1.0-1.5	150-300		3.0-5.0
Lidocaine				
Topical (OTC)	0.5%			
Topical (Rx)	5.0%			
Infiltration	0.5-1.0		300 (500)	0.5-1.0 (2.0-6.0)
Minor Nerve Blocks	1.0	50-200		1.0-2.0 (2.0-3.0)
Major Nerve Blocks	1.0-1.5		500	2.0-4.0
Epidural	1.0-2.0	150-500		0.5-1.5
Spinal	1.5, 5.0	30-100		0.5-1.5
Mepivacaine				
Infiltration	0.5-1.0		300 (500)	0.75-1.5 (2.0-6.0)
Minor Nerve Block	1.0	50-20		1.0-2.0 (2.0-3.0)
Major Nerve Block	1.0-1.5		500	3.0-5.0
Epidural	1.0-2.0	150-500		1.0-3.0
Spinal	4.0	40-80		0.5-1.5
Prilocaine				
Infiltration	0.5-1.0		500 (600)	0.5-1.5 (2.0-6.0)
Minor Nerve Blocks	1.0	50-200		1.0-2.0 (2.0-3.0)
Major Nerve Blocks	1.0-2.0		600	3.0-5.0
Epidural	1.0-3.0	150-600		1.0-3.0

Primary source: Strichartz and Berde (1994)
* Parenthetical data indicate solutions containing epinephrine.

8.0 REGULATORY STATUS

Local anesthetics are regulated by the Food and Drug Administration (FDA) under the authority of the Federal Food, Drug, and Cosmetic Act. U.S. government regulations pertaining to local anesthetics are summarized below. A special committee, Center for Drug Evaluations and Research – Anesthetic and Life Support Advisory Committee, was established in May 1978 to review and evaluate the use and safety of marketed and investigational drugs in the field of anesthesiology. However, this committee's authority is to expire on May 1, 2000, unless the Commissioner of Food and Drugs determines otherwise (Federal Register, 1998).

In 1997, the FDA, with assistance from its Scientific Advisory Committees and other outside consultants, the American Pediatrics Committee on Drugs, and consultants to the Pharmaceutical Manufacturer's Association developed guidelines for the clinical evaluation of new drugs which included local anesthetics (FDA, 1977).

In 1992, the Consumer Product Safety Commission (CPSC), under the authority of the Poison Prevention Packaging Act, published a Federal Register Notice to approve mandatory child-resistant packaging for all forms of lidocaine (>5.0 mg) and dibucaine (>0.5mg) available over-the-counter and by prescription. This action was in response to reports from the Poison Control Center of 750 cases of ingestion of lidocaine and dibucaine by children, resulting in 16 deaths and several cases of serious illness (CPSC, 1994). Some issues were raised about the technical feasibility of packaging some of the products for child-resistance; however, in 1994 the CPSC voted unanimously to require child-resistant packaging but to delay the final rulemaking until April 8, 1995. The effective date of the packaging requirements was April 10, 1996 (Federal Register, 1995).

In 1993, the FDA's Anesthetic and Life Support Advisory Committee voted 6-0 that evidence of carcinogenicity of the lidocaine metabolite 2,6-xylidine was in sufficient for labels to mention that it caused tumors in laboratory rats (Washington Drug Lett., 1993a; Anonymous, 1994). The Committee did want to wait for results of human liver slice studies before finalizing the vote.

The FDA now requires that products that may metabolize to aniline compounds carry a warning of carcinogenic risk in the package inserts (Nickel, 1996; Nickel, undated letter). These include formulations of EMLA, lidocaine, and prilocaine. These package inserts state that the metabolite of prilocaine, *o*-toluidine, has been found to be carcinogenic in both mice and rats,

and that 2,6-xylidine, the metabolite of lidocaine, was found to cause tumors in rats (Medical Economics Company, 1998; Health Central Online Pharmacy, 2000; Astra Pharmaceuticals, 1998).

Table 5. Regulations Relevant to Local Anesthetics

Regulation		Summary of Regulation
CPSC	CFR 16 Part 1700.14	Products containing more than 5 mg of lidocaine in a single package shall be subject to the provisions of Part 1700.14(a) and (b). The packaging is required to protect children from serious injury or illness due to exposure to the contents. A sample of the safety packaging is to be sent to the Consumer Product Safety Commission.
FDA	CFR 21 Part 2.110	This section pertains to products that pose a serious hazard to the public health. Since chlorofluorocarbons have been shown to deteriorate the ozone layer and consequently cause increased rates of skin cancer. All drugs that are contained in cans with chlorofluorcarbon propellants shall be subject to re-application as a new drug. "Anesthetic drugs for topical use on accessible mucous membranes of humans where a cannula is used for application" are exempt from this re-application process.
	CFR 21 Part 14.7c1	Establishes the Center for Drug Evaluations and Research – Anesthetic and Life Support Advisory Committee to "review and evaluate data on the safety and effectiveness of marketed and investigational human drugs for use in the field of anesthesiology and surgery. Effective May 1, 1978.
	CFR 21 Part 25.33	This section gives the FDA authority to enact and oversee food and drug policies in order to comply with the National Environmental Policy Act (NEPA) of 1969. "All agencies of the Federal Government must comply with section 102(2) of NEPA except where complience would be inconsistent with other statutory requirements". Veterinary anesthetic manufacturers are not required to submit an environmental impact statement or environmental assessment for the use of their products in animals.
	CFR 21 Part 310.545	This section lists certain ingredients that are present in over-the-counter (OTC) drug products and the intended uses of these products. However, there is not enough data available on these ingredients to establish the safety and effectiveness of these ingredients. Lidocaine is listed as an ingredient in poison ivy, poison oak, and poison sumac drug products. Lidocaine and lidocaine hydrochloride are listed as ingredients in oral health care products (nonantimicrobial).

Table 5. Regulations Relevant to Local Anesthetics (Continued)

Regulation		Summary of Regulation
F D A	CFR 21 Part 310.500	This section describes the conditions required to market the oral cardiac treatment drug, Digoxin. Digoxin labels contain a section on treatment of arrhythmias induced by digoxin. Lidocaine is listed as one of the drugs which has been approved for the treatment of digoxin intoxication.
	CFR 21 Part 333.120	Topical antimicrobial drug products and permitted combinations of active ingredients are described in this section. Provided that the antimicrobial drug product meets the test standards for potency and moisture set forth in CFR 21 Part 448.510a(b) any single generally recognized as safe amine or "caine" type local anesthetic may be used in combination with any of the following antibiotic(s): bacitracin ointment and Bacitracin-neomycin sulfate-polymixin B sulfate ointment. Provided that the antimicrobial drug product meets the test standards for potency and moisture set forth in CFR 21 Part 448.510e(b) any single generally recognized as safe amine or "caine" type local anesthetic may be used in combination with any of the following antibiotic(s): bacitracin-polymixin B sulfate topical aerosol and bacitracin zinc-neomycin sulfate-polymixin B sulfate ointment. Provided that the antimicrobial drug product meets the test standards for potency and moisture set forth in CFR 21 Part 448.513c(b) any single generally recognized as safe amine or "caine" type local anesthetic may be used in combination with any of the following antibiotic(s): bacitracin zinc-polymixin B ointment and neomycin sulfate-polymixin B sulfate cream.
	CFR 21 Part 346	Lidocaine (2-5%), Tetracaine (0.501%), and Tetracaine hydrochloride (0.5-1%) are listed as topical local anesthetic active ingredients in anorectal drug products for OTC use. These local anesthetic ingredients may be used in combination with other ingredients as set forth in 21 CFR, Part 346.22. These other ingredients include vasoconstrictors, antipruritics, keratolytics, astringents, and analgesics. This section also regulates the labeling of anorectal drug products.
	CFR 21 Part 348.10	Lidocaine is approved as an active ingredient in metered male genital desensitizer sprays at a concentration of approximately 10 mg per spray. Labeling requirements for these products are also set forth in this part.

Table 5. Regulations Relevant to Local Anesthetics (Continued)

Regulation		Summary of Regulation
FDA	CFR 21 Part 369.20	The recommended warning and caution statements for external local anesthetics are set forth in this part. The product label should read: *Caution*-Do not use in the eyes. If the condition for which this preparation is used persists or if a rash or irritation develops, discontinue use and consult a physician.
	CFR 21 Part 448.510	States that certain antibacterial formulations containing bacitracin may also contain "a suitable local anesthetic". See also CFR 21 Part 333.120
	CFR 21 Part 522	Any new animal drug in an injectable or implantable form is listed in this section. A new animal drug is one: that is intended for use in any animal other than man or is included in animal feed, whose composition is not generally regarded as safe and effective under the conditions prescribed, recommended or suggested in the labeling thereof that has been tested in laboratory investigations for a certain use in animals but has not been used for that intended purpose for any length of time. Lidocaine injection with epinephrine is listed in Part 522.1258. Its sponsor was Steris Laboratories, Inc., located in Phoenix, AR. Mepivacaine hydrochloride injection is listed in Part 522.1372. Its sponsor was Pharmacia & Upjohn Co., located in Kalamazoo, MI. Sodium pentabarbital with "a local anesthetic" is listed in Part 522.1704. Its sponsor was Schering-Plough Animal Health Corp., located in Union, NJ. The dosing as well as labeling requirements are also listed for each new drug
	CFR 21 Part 524.390c and 524.1484b,c,d,f,k	Lists dosages for ophthalmic and topical new animal drugs. The products are for the treatment of dermatitis and external ear conditions (ototis externa) in animals and usually contain between 4.2 and 5.0 mg of tetracaine. The sponsors as well as the application and labeling criteria for each product are also described.
	CFR 21 Part 862.3555	A lidocaine test system is described. It is "a device intended to measure lidocaine, an antiarrythmic and anticonvulsive drug, in serum and plasma". Measurements taken by this device are used to diagnose and treat lidocaine overdose and to monitor lidocaine concentrations during therapy.

9.0 TOXICOLOGICAL DATA

9.1 General Toxicology

9.1.1 Human Data

Local anesthetic drugs are potentially toxic if they are administered in high doses or into the wrong anatomic site, reaching the major target organs of toxicity, the brain and heart (Feldman, 1994; Strichartz and Berde, 1994; Gotta et al., 1998). Local anesthetic toxicity results from the interaction of many factors such as the rate and route of administration, preexisting medical conditions, acid-base balance, and age, and physicochemical properties such as lipid solubility, pK_a, and route of metabolism (Feldman, 1994).

Systemic reactions to local anesthetics mainly involve the central nervous system (CNS) and the cardiovascular system (CVS), where the former has been observed to be more susceptible to the systemic actions of the drugs in both humans and animals. Therefore, a lower dose and blood level of local anesthetic produces CNS toxicity versus that resulting in circulatory collapse (Strichartz and Berde, 1994).

Systemic toxicity shares a parallel relationship with relative anesthetic potency, which is based on the amount of drug required to produce an equivalent neural blockade. For the amides, prilocaine, lidocaine, and mepivacaine have a relative potency of 2; etidocaine, 6; ropivacaine, 7; and bupivacaine, 8. Because the amino ester agents are rapidly hydrolyzed in the blood and the amino amide local anesthetics are mainly metabolized in the liver, the toxic effects of the former occur for shorter periods of time (Feldman, 1994).

9.1.1.1 Central Nervous System Toxicity

Within the CNS, toxicity ranges from excitation to convulsions (Gotta et al., 1998). Early symptoms of CNS toxicity are feelings of lightheadedness, drowsiness, nervousness, and tongue or circumoral numbness, followed by visual and auditory disturbances, slurring of speech, and tinnitus. Other symptoms include disorientation, vomiting, sensations of heat, and irrational conversation. Objective signs of CNS toxicity include shivering, muscular twitching, and tremors (Feldman, 1994; Strichartz and Berde, 1994; Noven, 1997). These initial signs and symptoms of CNS toxicity may also be followed by seizures, respiratory arrest, myocardial depression, and even death (Feldman, 1994). If the local anesthetic is administered rapidly by i.v. injection or given as a sufficiently large dose, CNS depression immediately follows

excitation (Strichartz and Berde, 1994). These effects seem to indicate that local anesthetics exert a dose-dependent and blood concentration-dependent action on the system. There is a sedative state at very low doses, an excitatory state at higher doses (seizures), and finally a state of complete depression (coma). At very critical, low concentrations, local anesthetics can serve as effective anticonvulsant agents (Feldman, 1994). Toxic effects are seen at plasma levels of 5-10 µg/mL for lidocaine, mepivacaine, and prilocaine and 1.5-4 µg/mL for bupivacaine, etidocaine, and ropivacaine (Gotta et al., 1998).

The human therapeutic, toxic, and comatose-fatal blood-plasma/serum concentrations of the local anesthetics discussed in this report are presented in **Table 6**, while the maximum tolerated dose and i.v. convulsive dose are presented in **Table 7**.

CNS toxicity usually occurs before and therefore is a good warning of CVS toxicity induced by local anesthetics (Gotta et al., 1998).

Table 6. Human Therapeutic, Toxic, and Comatose-Fatal Blood-Plasma/Serum Concentrations of Local Anesthetics

Compound	Blood-Plasma/Serum Concentrations (µg/mL)			$t_{1/2}$ (hr)[a]
	therapeutic (from)	toxic (from)	comatose-fatal	
Bupivacaine	(0.25-) 0.5-1.5 (-2)	2.4		0.5-3
Etidocaine	1-1.5	1.6-2		2.3
Lidocaine	(1-) 1.5-5[b]	6-7	10	1-4[b]
Mepivacaine	~0.4	5-6 (-10)		1-3
Prilocaine	0.5-1.5 (-2)[c]	5-6	~20	1-2
Ropivacaine		(1-) 2[d]		2[e]

[a] terminal elimination half-life
[b] higher and increased, respectively, in patients with impaired hepatic function; for tinnitus aurium: therapeutic plasma concentration ~1-2 µg/mL
[c] 3-7 minutes after retrobulbar blockade: 0.5-1.1 µg/mL
[d] after intravenous application; $t_{1/2}$: 4-7 hours following epidural administration (~4-5 hours following intercostal block and ~8 hours following brachial plexus blockade)
[e] mild CNS symptoms (limited data)

Source: Schulz and Schmoldt (1997)

Table 7. Maximum Tolerated and Convulsive Doses of Local Anesthetics in Humans

Compound	Route	Toxicity	Dose (mg/kg)	Plasma Concentration (µg/mL)
bupivacaine	i.v.-inf	MTD	~1.4-1.6	1.2-2.2
etidocaine	i.v.-inf (20/mg/min) i.v.-inf (10/mg/min)	MTD MTD	2.3 3.4	2.27 -
lidocaine	i.v.-inf i.v.	MTD CD	6.4 7.33	5.3 -
mepivacaine	i.v.-inf	MTD	9.8	-
ropivacaine	i.v.-inf	MTD	1.7	1.70

Abbreviations: CD = dose to cause convulsion; i.v. = intravenous; i.v.-inf = intravenous infusion; MTD = maximum tolerated dose. Source: Feldman (1994)

9.1.1.2 Cardiovascular System Toxicity

Local anesthetics can have a direct effect on both the heart and peripheral blood vessels (Strichartz and Berde, 1994). They have a suppressant effect on the heart, causing a reduction in myocardial contractile force and extension or block of intracardiac conduction. Local anesthetics can also act as vasodilators; high doses cause a reduction in heart rate and blood pressure, cardiac conduction defects, and arrhythmias. However, some local anesthetics have induced sudden cardiovascular collapse, ventricular arrhythmias and fibrillation, and even death in humans [and animals], particularly with the potent, highly lipid-soluble, highly protein-bound agents, such as bupivacaine and etidocaine. Numerous studies indicate that bupivacaine is the most cardiotoxic local anesthetic (Feldman, 1994).

The primary cardiac electrophysiologic effect of local anesthetics is a lowering of the maximum rate of depolarization in Purkinje fibers and ventricular muscle. The drugs can also exert effects on the mechanical activity of cardiac muscle, specifically a dose-dependent negative inotropic action, which is proportional to the conduction blocking potency of the local anesthetics in isolated nerves. The more potent agents (bupivacaine and etidocaine) decrease cardiac contractility at the lowest concentration, while the intermediate potent local anesthetics (lidocaine, mepivacaine, and prilocaine) do so at a higher concentration (Strichartz and Berde, 1994).

On peripheral vascular smooth muscle, local anesthetics exert a biphasic effect. *In vivo* studies have shown that small doses of local anesthetics decrease peripheral arterial flow without

any change in arterial blood pressure, while large doses increase blood flow (Strichartz and Berde, 1994).

Just as local anesthetics can serve as anticonvulsant agents at certain doses, they can also act as antiarrhythmic agents at certain doses. Lidocaine, probably the most effective antiarrhythmic agent, has been employed for 30 years (Feldman, 1994).

9.1.1.3 Local Neurotoxicity

Neurotoxicity can be affected by factors such as pH, additives or preservatives, and concentration of the local anesthetic. Almost all clinically used drugs result in some type of neurologic deficit. Clinically, local neurotoxicity can occur after an accidental subarachnoid injection of an epidural dose of a local anesthetic; up to 30 mL of anesthetic solution can be injected inadvertently into the subarachnoid space. Signs and symptoms include prolonged sensory or motor deficit or even permanent neurologic deficit (Feldman, 1994).

9.1.1.4 Local Tissue Toxicity

Clinically used local anesthetics rarely produce localized nerve damage. Intramuscular (i.m.) injection of local anesthetics has resulted in skeletal muscle changes. The more potent, longer-acting drugs (bupivacaine and etidocaine) were observed to cause more localized skeletal muscle damage versus the less potent, shorter-acting ones (lidocaine, mepivacaine, and prilocaine). The damage was reversible, with muscle regeneration complete within two weeks following injection of the local anesthetic (Strichartz and Berde, 1994).

9.1.1.5 Reproductive and Teratologic Effects

Intracervical and intraspinal administration of bupivacaine to women have resulted in specific developmental abnormalities in the CVS and in behavioral and other postnatal effects on the newborn, respectively (RTECS, 1999).

Although there are no *adequate* studies of lidocaine in pregnant women, parenteral administration of the local anesthetic to women have shown specific developmental abnormalities in the CNS (Noven, 1997; RTECS, 1999). In two human male subjects given 1% lidocaine hydrochloride into the base of each cavernosum during a routine circumcision, impotence resulted (HSDB, 1999).

The primary source of epidemiological data on potential teratogenic effects of local anesthetics is the Collaborative Perinatal Project. When 947 women were exposed to lidocaine during pregnancy, the frequencies of congenital anomalies in general, of major and minor malformations, and of major classes of congenital anomalies among the children born were not increased (0.99); in 293 women exposed in the first four lunar months, the relative risk for malformation was only 0.54 (Heinonen et al., 1977; cited by Friedman, 1988, and Shepard, 1999a). When 224 women were treated with mepivacaine during pregnancy, the frequency of congenital anomalies among the children born was no greater than expected. When 82 women were treated with the drug during the first four lunar months of pregnancy, a twofold increase in the frequency of congenital anomalies was seen; eight women showed malformations (Heinonen et al., 1977; cited by Friedman, 1988, and Shepard, 1999b).

Bupivacaine, etidocaine, prilocaine, and pyrrocaine have not been adequately studied for teratogenic effects. There are no reports of congenital anomalies in children born to women who had these drugs administered during pregnancy (Friedman, 1988; TERIS, 1998).

9.1.1.6 Neonatal Effects

Acid-base status, Apgar scores, and neurobehavioral assessments have shown that local anesthetics have negligible effects on the neonate (Santos et al., 1994; cited by D'Alessio and Ramanathan, 1998). However, significant behavioral differences between infants (aged 20 hours to six days) exposed to local anesthetics during gestation and unexposed infants have been observed. In a study testing neonatal visual pattern preference, the total looking times of exposed infants were almost 50% greater than those of unexposed infants. Additionally, a significant difference in preference for some pairs of the visual stimuli was seen (Blair et al., 1984).

Studies on whether epidural anesthesia adversely affects newborn behavior have been and continue to be conflicting. In one study using bupivacaine, neonates were found to habituate and orient better to inanimate auditory stimuli at one day of age. In other studies, poor motor organization and/or regulation of state during the first three days of life were observed (King, 1997). At one month, babies were less adaptable, less alert, less able to orient, more intense, more irritated, and had decreased appetite and poor interactive ability (Murray et al., 1981; Sepkoski et al., 1992; both cited by Walker, 1997). They were found to remain depressed on a

number of alerting and orienting skills up until the first six weeks of life (Rosenblatt et al., 1981; cited by Walker, 1997).

Infants born from mothers receiving continuous lumbar epidural blocks with lidocaine or mepivacaine scored significantly lower on tests of muscle strength and tone (head control, arm recoil, truncal tone, and general body tone) but not on those evaluating habituation to repeated stimulation (e.g., light or sound) during the first eight hours of life. The mean concentration of mepivacaine in the umbilical arteries of infants in the epidural-block group were 1.68 µg/mL at birth and 0.82 µg/mL at eight hours of age. For lidocaine, the values were 0.48 µg/mL and 0.13 µg/mL, respectively (Scanlon et al., 1974). More recent studies with the commonly used local anesthetics alone, or in combination with narcotics such as fentanyl and sufentanil, have reported no such effects. For example, Kangas-Saarela et al. (1989; cited by D'Alessio and Ramanathan, 1998) showed that infants of mothers who received epidural analgesia for labor were more alert at 3 hours, 2 days, and 4 to 5 days of age compared with those whose mothers received no analgesia.

9.1.1.7 Methemoglobinemia

Large doses of prilocaine have resulted in the development of methemoglobinemia; in general, at least a 600-mg dose is needed to produce clinically significant levels when administered epidurally in adults. The metabolism of prilocaine in the liver results in the formation of *o*-toluidine, which is responsible for the oxidation of hemoglobin to methemoglobin (Strichartz and Berde, 1994). Peak values of methemoglobin were reached six hours after administration of prilocaine, but methemoglobin disappeared after 24 hours in most patients. The duration and intensity of cyanosis correlated with the duration and extent of methemoglobinemia (Hjelm and Holmdahl, 1965). With the formation of methemoglobin, anoxia, along with painful hematuria, was observed in individuals exposed to the metabolite (NIOSH, 1978; Hiles and Abdo, 1990).

Lidocaine and xylidine intoxication has also produced methemoglobinemia (IARC, 1993; NIOSH, 1978). In contrast to prilocaine, single doses of lidocaine (500 mg) produced detectable amounts of methemoglobin (0.4-2.7%) but no cyanosis (Hjelm and Hulmdahl, 1965; cited by Luduena, 1971). Mepivacaine may induce methemoglobinemia as well as cyanosis (Vourc'h, 1971).

Section 9.1.1.8 presents further details on this topic in newborn infants.

9.1.1.8 Methemoglobinemia and EMLA Cream

Methemoglobin was detected in the blood of infants whose mothers were given epidural analgesia with prilocaine for delivery (Climie et al., 1967; cited by Vourc'h, 1971).

In neonates undergoing circumcision, application of 5% lidocaine-prilocaine cream (EMLA) resulted in no adverse effects (i.e., methemoglobinemia). Mild pallor at the application site was observed in 32% of the subjects. One neonate had mild edema, and one had a local infection. Sixty-one percent of the neonates had detectable plasma lidocaine concentrations, while 55% had detectable plasma prilocaine concentrations; highest measurements were made within four hours after administration. Other studies using pre-term and full-term neonates have also found no methemoglobinemia with single applications of lidocaine-prilocaine cream (Taddio et al., 1997). For example, when applied to term neonates under the age of three months for one hour on the back of the hand or on the cubital area under occlusion, 1 g of EMLA 5% only produced a high frequency of mild to moderate local pallor, which was not clinically significant (Brisman et al., 1998). The only two reported cases of methemoglobinemia in infants exposed to EMLA occurred with high doses (Taddio et al., 1997).

The combined use of EMLA cream (containing 12.5 mg prilocaine) and caudal anesthesia (5.4-6.7 mg/kg prilocaine) for herniotomy in premature infants resulted in toxic methemoglobinemia. The highest methemoglobin concentration (30.6%) was observed 5.5 hours after anesthesia. All infants had mottled skin, poor peripheral perfusion, and were pale and cyanotic; the symptoms were most severe between three and eight hours and disappeared 10-20 hours after caudal anesthesia (Frey and Kehrer, 1999).

Additionally, application of EMLA has produced blanching in healthy volunteers (HSDB, 1999).

9.1.1.9 Toxicity of Regional Versus General Anesthesia

Regional anesthesia is preferred to general anesthesia during labor because of the fewer maternal deaths and serious injuries that occur. Although little, if any, adverse effects are observed in the fetus or the neonate, generally the sicker the fetus, the greater the benefit of regional anesthesia over general anesthesia. The toxic effects of regional anesthesia using amide

local anesthetics on the fetus are primarily caused by maternal hypotension and seizures; effects of local anesthetics on the newborn infant are minimal and short-lived. General anesthesia results in brief, minimal depression of the healthy term neonate, and performing it requires many more factors to consider versus regional anesthesia, such as the larger numbers of drugs administered and doses and induction-delivery time. Furthermore, the chance of neonatal Apgar scores being lower and respiratory depression is higher with general anesthesia. However, in the healthy parturient and fetus, minor differences in neurobehavioral scores are obtained under both general and regional anesthesia (James, 1997; D'Alessio and Ramanathan, 1998).

9.1.1.10 Immunotoxicity

Although allergic reactions to local anesthetics are extremely rare, amino ester drugs such as procaine, chloroprocaine, and tetracaine, which are derivatives of *p*-aminobenzoic acid, a known allergen, may produce allergic-type reactions. The majority of these reports were of positive skin reactions, particularly with their use in dentistry. In a study using patients believed to have no history of local anesthetic allergy, interadermal injections of amino ester drugs produced positive skin reactions in 30% of the population, while amino amide drugs showed no such results. Using patients with a history of alleged allergy, doses of procaine, tetracaine, or chloroprocaine gave positive skin reactions, while lidocaine, mepivacaine, or prilocaine did not (Feldman, 1994; Strichartz and Berde, 1994). Allergic reactions include cutaneous lesions, urticaria, pruritis, edema, hypotension, asthma, nausea and vomiting, and anaphylactoid reactions (Vourc'h, 1971; Noven, 1997).

The few occurrences of allergic reactions to amino amide local anesthetics have been linked with the presence of methylparaben, a preservative used in some commercial preparations of the agents and a compound that is chemically related to *p*-aminobenzoic acid and also a known allergen (Feldman, 1994).

The effect of local anesthetics on human natural killer (NK) cell activity *in vitro* depends on the anesthetic agent used. For example, lidocaine, in contrast to bupivacaine and mepivacaine, has been found to significantly inhibit NK cytotoxicity at low concentrations (Mitsuhata et al., 1991; cited by De Amici et al., 1999). A recent study has shown that the cord blood NK activity is markedly influenced by the method of delivery. In newborns delivered by elective cesarean section under epidural anesthesia (lidocaine hydrochloride with epinephrine),

NK cell activity was significantly lowered compared to those delivered by elective cesarean section without labor under general anesthesia (thiopentone) but similar to those delivered vaginally with uncomplicated labor (no analgesia). With K562 (human erythroleukemia) lines used as the target cells and cord blood lymphocytes as the effector cells, NK cell activity was measured at effector:target ratios of 10:1, 30:1, and 100:1. The values for lymphocytes from the group of newborns delivered by cesarean section under epidural anesthesia were 10.9, 21.2, and 31.6% lysis, respectively. With delivery by cesarean section under general anesthesia, the NK activity was 20.1, 35.1, and 52%, respectively, and with vaginal delivery, the values were 11.9, 19.6, and 33.3%, respectively. A significant correlation between lidocaine concentration and NK activity was not seen. The mean lidocaine blood concentration in the newborns delivered by cesarean section under epidural anesthesia was 414.1 µg/L; no lidocaine was detected in the other two groups (De Amici et al., 1999).

Lidocaine has also been observed to inhibit neutrophil chemotaxis and other immune functions in adults (Sasagawa, 1991; cited by Gasparoni et al., 1998). In newborns born by cesarean section with epidural lidocaine anesthesia, neutrophil chemotaxis levels were significantly lowered (35.51 µm) compared to those delivered by cesarean section with general anesthesia (nitrous oxide) (71.43 µm) and those delivered vaginally without any analgesia (54.6 µm). In addition, a significant inverse relationship between chemotaxis and lidocaine levels in infants born by cesarean section after epidural anesthesia was observed. A mean serum lidocaine concentration of 377.6 µg/L was found; in the other two groups, lidocaine was not detected (Gasparoni et al., 1998).

9.1.2 Disposition, Metabolism, and Pharmacokinetics

9.1.2.1 General Discussion

9.1.2.1.1 Mode of Action of the Amide Local Anesthetics

A typical peripheral nerve consists of multiple bundles of axons (fascicles). Each bundle of axons is held together by the endoneurium and wrapped in a membrane called the perineurium. Several perineurium bound axon bundles are held together by the epineurium. An axon (nerve fiber), with its own cell membrane, is encased in a Schwann cell sheath that has its own membrane. The majority of large motor and sensory nerve fibers are encased in multiple layers of specialized Schwann cells, called myelin. The myelin serves as an insulator from the

surrounding salt medium and greatly increases the speed of nerve conduction through the axoplasm. There are periodic interruptions in the myelin sheath around the axons. These interruptions are known as the nodes of Ranvier and it is here that the Na^+ channels for nerve impulse and propagation are located. There are some nonmyelinated axons, such as autonomic postganglionic C fibers, which have ion channels distributed all along the axon (Strichartz and Berde, 1994).

Nerve conduction occurs by altering the neural membrane permeability of sodium and potassium ions into the axon at the ion channels, creating an electrochemical potential. Local anesthetics work by reaching the nerve axon and interfering with the function of the ion channels that control nerve impulse propagation. It appears that there is a single site for local anesthetic binding on the sodium channel, and by binding there, conformational changes occur in the channel proteins which prevent opening of the channel. The speed at which this occurs is dependent on the local anesthetics hydrophobicity of the base and cation species and the pK_a . For an anesthetic molecule to reach this site of action, it must traverse the multiple lipid membranes and connective tissue of the nerve (Strichartz and Berde, 1994).

It is not clear which form of the local anesthetic, cation or neutral base, is most responsible for anesthesia. The neutral base in the axonal external medium may be the active species or membrane penetration and transport, with the favored permeability of neutral base over charged ion, may be essential for channel blocking . Another possibility is that cationic species may be acting from the cytoplasmic surface as a result of direct control of axoplasmic pH or internal perfusion with permanently charged quaternary amine homologues (Strichartz and Berde, 1994).

9.1.2.1.2 Structural and Physical-Chemical Properties and Their Relation to Pharmacokinetics

The potency and duration of action of the local anesthetics are primarily related to the physical-chemical properties and structure of the local anesthetic, respectively. The amide local anesthetics are weak bases that are variably lipophilic. The more highly substituted the alky or tertiary amines on or near the tertiary amine or in the aromatic ring, the more lipophilic the anesthetic. It is the lipophilicity, measured by the octanol/aqueous buffer partition coefficient, that positively correlates the anesthetic potency (Strichartz and Berde, 1994). This is because

lipophilic compounds penetrate nerve membranes more readily than hydrophilic compounds, resulting in a greater concentration of the drug at the interior sodium ion channel receptor (Lenz et al., 1992). In clinical trials, the correlation of hydrophobicity to anesthetic potency is not as clear as *in vitro* results and may be due to such factors as vasodilation caused by the anesthetics themselves and tissue redistribution of anesthetic (Strichartz and Berde, 1994; Lenz et al., 1992).

The amount of un-ionized and ionized forms of a local anesthetic in solution are represented by the pK_a. The pK_a is the pH at which there are equal molar concentrations of the un-ionized (B) and ionized (BH^+) form of the local anesthetic, and this relationship is represented by the following equation:

$$[BH^+]/[B] = 10^{(pKa - pH)}$$

The pK_a can shift due to certain environmetal factors such as temperature and ionic strength as well as the medium surrounding the drug (Sanchez et al., 1987; cited by Strichartz and Berde, 1994). In the apolar membrane, the average pK_a is lower than that in solution so that the concentration of the un-ionized base is 10 times the concentration of the ionized cations (Schreier et al., 1984; cited by Strichartz and Berde, 1994). As the pH of the medium is increased above the pK_a, then the equilibrium shifts towards a greater concentration of the base form (Strichartz and Berde, 1994). If the pH decreases due to addition of acid or CO_2, the water solubility increases (Widman, 1975). Local anesthetics with low pK_as, such as lidocaine, generally have a more rapid onset of anesthesia due to the high concentration of the un-ionized form of the drug at physiologic pH. This allows for more of the un-ionized form to accumulate in the site of action (Glazer and Portenoy, 1991). Bupivacaine is one of the most potent local anesthetics. It has a relatively moderate-to-long duration of onset due to its moderate pK_a. Because of bupivacaine's high affinity for protein binding, it is held in the neural membrane longer and more tightly than other local anesthetics, resulting in a longer and more profound sensory inhibition (Lenz et al., 1992)

Etidocaine and bupivacaine are much more potent (longer acting and greater degree of anesthesia) than lidocaine and mepivacaine (Scott, 1975; cited by Tucker et al., 1977). The structure of the local anesthetics, rather than physical-chemical properties, have the greatest influence on their clearance and metabolism by the liver (Tucker et al., 1977). For example, cyclization of the N-alkyl chain retards the net metabolism and hepatic clearance of the anesthetics (Tucker, 1975; cited by Tucker et al., 1977).

Table 8. Relative *In Vitro* Conduction Blocking Potency and Physical-Chemical Properties of Local Anesthetics

Anesthetic	Relative Conduction Blocking Potency[a]	pK_a (25 °C)	pK_a (36 °C)	Lipid Solubility (25 °C)	Hydrophobicity[b] (36 °C)
Mepivacaine	1.5	7.9	7.7	21	130
Prilocaine	1.8	8.0	8.0	25	129
Lidocaine	2	8.2	7.8	43	366
Ropivacaine	7	8.2	□	115	□
Bupivacaine	8	8.2	8.1	346	3,420
Etidocaine	8	8.1	7.9	800	7,320

Sources: Strichartz and Berde (1994) and Strichartz et al. (1990; cited by Feldman, 1994).
[a] Data derived from C fibers of isolated rabbit vagus and sciatic nerve
[b] Hydrophobicity equals octanol/buffer partition coefficient of the base; ratio of concentrations

9.1.2.1.3 Absorption of Amide Local Anesthetics

Absorption and distribution of amide local anesthetics varies depending on many factors, such as site and method of administration, blood flow characteristics, plasma protein binding, plasma pH, and the physical properties of the local anesthetic (i.e., pK_a, hydrophobicity, etc.).

Absorption from the site of injection depends on the blood flow□the higher the blood flow the more rapid the rate at which plasma concentrations increase and the greater the peak plasma concentrations of the drug (Arthur et al., 1993). Delaying absorption of local anesthetics from the site of application into the blood can result in a considerable decrease in the toxicity (Luduena et al., 1971). Theoretically, a person with a cardiac output of 4 L/min injected i.v. with 400 mg of a drug for 1 minute would have a peak plasm concentration of 100 µg/mL (Arthur et al., 1993). When a local anesthetic is injected, the rate of absorption is greatest after intercostal block, followed by epidural, brachial plexus, and lower limb blocks, with subcutaneous (s.c.) infiltration being the slowest (Arthur et al., 1993). If vasoconstrictors, such as epinephrine, are administered with the local anesthetic, then absorption is reduced, usually allowing the safe dose of the anesthetic to be increased by 50-100%.

Subcutaneous and dermal application of the local anesthetics results in prolonged persistance of the local anesthetics at the site of application (prilocaine and lidocaine in this

report). Local anesthetics do not readily penetrate healthy human skin in their salt form; however, effects may be seen if applied in their base form (Leopold and Maibach, 1999). Dermal absorption will be affected by the vehicle that contains the local anesthetic. The maximum anesthetic effect was observed one hour after application of lidocaine. The onset of anesthetic action after dermal application can be correlated with the local anesthetics solubility in medium chain triglycerides which has properties similar to stratum corneum lipids. Dermal absorption of local anesthetics is affected by the vasculature of the area of application, age of the patient and condition of the skin. Lidocaine plasma concentrations after dermal application have been observed to peak 32 hours or longer after application. In neonates, dermal absorption is more rapid due to the immaturity of the skin, which behaves more like a mucous membrane (Essink-Tebbes et al., 1999).

Absorption from the epidural space after epidural administration of local anesthetics is much slower than after i.v. administration (Katz et al., 1993). This may be due to the effect of the anesthetic on the local tissue vasculature. Bupivacaine and lidocaine have both been shown to produce vasodilation at the area of administration, thereby increasing the rate of absorption to the bloodstream from the site of administration (Katz et al., 1993). Another factor which may contribute to the slower absorption of the local anesthetics from the epidural space is its high fat content. The more lipid soluble compounds, such as bupivacaine and ropivacaine, are released more slowly from the epidural space than the less lipid soluble anesthetic lidocaine (Katz et al., 1993). The absorption of the local anesthetics from the epidural space is biphasic, with an initial rapid phase followed by a slower terminal phase (Katz et al., 1993; Tucker and Mather, 1975; Burm, 1989).

After a local anesthetic reaches the circulatory system, it will pass through the right side of the heart, then to the lungs, and finally to the organs with high blood flow and high affinity—the brain, heart, kidney, liver, and spleen (Hansson, 1971; Arthur et al., 1993). After a small i.v. bolus dose of lidocaine (0.5 mg/kg) in volunteers and patients, it was found that as much as 50 to 70% of the dose was taken up by the lungs on first pass and that uptake in patients with lung insufficiency was not markedly different (Jorfeldt et al., 1979, 1983; cited by Burm, 1989). Lung uptake is promoted by the relatively low pH of the fluid in the lungs when compared to plasma (Burm, 1989). A pH decrease in the cells of the lungs may result in diffusion trapping, a condition in which the transmembranous passage of local anesthetics in

their un-ionized form is followed by dissociation in partially ionized components in the cell (Catchlove, 1972; cited by Widman, 1975). This trapped, dissociated, anestheticly active form may then cause unexpected toxic reactions (Widman, 1975). This is important when giving anesthetics as an antiarrythmic, considering that circulation will be impaired and acidosis is a likely result. The lungs may temporarily sequester, and possibly metabolize, large amounts of local anesthetics; however, as the dose increases, the distribution decreases so that the lungs may not be able to prevent a toxic reaction should a rapid i.v. injection be given (Arthur et al., 1993). A small fraction of the anesthetic dose may distribute slowly into the fat and muscle because of their low blood supply; but because of the hydrophobicity of the local anesthetics, there could be absorption and temporary storage in the fat before redistribution into the blood stream (Arthur et al., 1993). Children, especially infants, have more rapid heart rates and may predispose to accumulation of bupivacaine in the myocardium (Badgewell et al., 1990b; cited by Brown et al., 1999). One must still remember that the distribution characteristics of the amide local anesthetics are similar because greater tissue affinity of the more lipophilic anesthetics, bupivacaine and etidocaine, is offset by extensive plasma protein binding (Burm, 1989).

Epinephrine (adrenalin) can be administered concomitantly with a local anesthetic to prolong the duration of anesthetic action, as well as reduce the absorption of the local anesthetic to the blood stream, thereby keeping the maximum plasma concentration of the local anesthetic low and decreasing the risk of systemic toxicity (Löfström, 1971). The addition of epinephrine to the anesthetic dose can decrease plasma concentrations of the local anesthetic by as much as 50%, as in the case of bupivacaine (Reynolds et al., 1989). In short-acting local anesthetics, such as lidocaine, epinephrine may prolong the duration of anesthesia fourfold; however, the addition of epinephrine in long-acting local anesthetics such as bupivacaine did not significantly increase the duration of anesthetic effect (Löfström, 1971). In obstetric medicine, epinephrine has ✂- and ✍-adrenoreceptor stimulating properties, which may increase the tonus of the myometrial muscle and weaken myometrial contractility, thereby reducing uterine blood flow and prolonging delivery (Ralson and Schnider, 1978; cited by Schierup et al., 1988).

Local anesthetics, like most drugs, will bind to plasma proteins to some degree. The two serum proteins involved with amide local anesthetics are α_1-acid glycoprotein and albumin (Arthur et al., 1993). α_1-Acid glycoprotein readily binds drugs but has a limited capacity for them, but albumin has a low affinity and a large capacity. As the concentration of a local

anesthetic in serum increases, the percentage that is bound to the two proteins decreases (**Table 9**) (Arthur et al., 1993). Attempts have been made to correlate local anesthetic toxicity with protein-binding characteristics; however, the assumption that greater protein affinity resulted in less tissue absorption and hence less toxicity was not true. In two separate studies, it was found that alteration of the plasma protein concentrations did not attenuate the accumulation of lidocaine or bupivacaine in the brain of rats (Pardridge et al., 1983; Terasaki et al., 1986). Denson et al. (1984) showed that protein binding is usually measured *in vitro* under equilibrium conditions and is very different from the conditions of rapid absorption in humans. Also, the bound drug in plasma is in equilibrium with the unbound, so that drug from either fraction is able to diffuse down a concentration gradient and bind to tissue. This is evident with prilocaine, which has the lowest protein affinity in serum, but has the least toxicity. This low toxicity could be due to low binding to nerve cell protein (Arthur et al., 1993). While protein binding may not be important in determining the diffusion of amide local anesthetics into tissue, it is one of the most important factors determining the transfer of local anesthetics across the placenta.

Table 9. Approximate Percentages of Local Anesthetics That Are Protein-Bound at Two Different Serum Concentrations

Local Anesthetics	Percent Bound	
	1 µg/mL serum	50 µg/mL serum
Bupivacaine	95	60
Etidocaine	95	60
Ropivacaine	94	63
Lidocaine	70	35
Mepivacaine	75	30
Prilocaine	40	30

Source: Arthur et al. (1993)

Differences in the amount of α_1-acid glycoprotein in various types of patients will affect the concentration of free local anesthetic in plasma. For example, neonates have a very low concentration of α_1-acid glycoprotein in plasma and will have much higher free local anesthetic fractions (Tucker, 1994). Plasma binding of bupivacaine and lidocaine in the human neonate is about 50% of that found in an adult (Tucker et al., 1970; cited by Pedersen et al, 1982). However, the total body clearance of local anesthetics in the neaonte and the greater volume of

distribution may offset the low plasma binding (Pedersen et al., 1982). Patients with inflammatory disease, cancer, postmyocardial infarction, and post-operative patients have a higher concentration of binding protein, resulting in lower free drug fractions (Tucker, 1994).

9.1.2.1.4 Pharmacokinetics of Amide Local Anesthetics

The elimination of local anesthetics from plasma is characterized by biphasic elimination, an □-phase and a □-phase. The □-phase is characterized by the rapid absorption of the anesthetic by the organs and tissue and is measured by the □-phase half-life ($T_{1/2\beta}$). The $T_{1/2\beta}$ of the amide local anesthetics is so rapid that it is usually less than 6 minutes (Caldwell et al., 1976 abstr.). However, once the tissues become "saturated" with the maximum concentration of local anesthetic, then the elimination of the local anesthetic rapidly decreases until it approaches the $T_{1/2\beta}$. The $T_{1/2\beta}$ is the total body clearance of the local anesthetic due to hepatic extraction and excretion. The $T_{1/2\beta}$ is under the influence of plasma protein binding of the local anesthetic, as well as hepatic clearance.

Because the amide local anesthetics have a stimulant effect on the circulatory system, systemic accumulation may be accompanied by increases in heart rate, cardiac output, and hepatic blood flow. Since the kinetics of these drugs is perfusion limited, then cardiovascular effects can be expected to influence their absorption and disposition by feedback (Tucker et al., 1977).

The placental transfer of the local anesthetics by passive diffusion is affected by the drug's molecular weight, lipid solubility, pK_a, protein binding, fetal pH, and fetal absorption (Banzai et al., 1995; Johnson et al., 1995 abstr.). The amide local anesthetics readily cross the placenta by passive diffusion in the unbound un-ionized form (Reynolds, 1979; cited by Hamshaw-Thomas and Reynolds, 1985). Studies have shown that the cord-to-maternal plasma concentrations of local anesthetics equilibrate quickly across the placenta and reaches a relatively constant level 15-30 minutes after adminstration to the mother due to the high lipid solubility of the un-ionized form and their low molecular weight (Tucker, 1994; Terama and Rajamäki, 1971). The rate of transfer of a drug across the placenta is measured by the umbilical venous/maternal venous ratio (UV:MV) upon administration of the drug, and while fetal tissue saturation is incomplete, the umbilical artery/maternal venous (UA:MV) concentration ratio should increase to reach a plateau that approaches the UV:MV (Reynolds et al., 1989). During

maternal drug absorption, a small gradient may exist if there is fetal metabolism. Both UV:MV and UA:MV are affected by transplacental pH and governed by the gradient of transplacental □-glycoprotein (Petersen et al., 1981; O'Brien et al., 1982; Kennedy et al., 1979; all cited by Reynolds et al., 1989; Hamshaw-Thomas and Reynolds, 1985). The main cause of interindividual variation should be overcome by examining the UA:UV ratio which gauge the extent of fetal equilibration and is not affected by □-glycoprotein concentrations (Reynolds et al., 1989). The decreased amount of protein binding in the fetus and neonate would likely result in greater volume of distribution and may contribute to the reduced rate of elimination in the fetus (Morgan et al., 1978). Elimination half-live of the local anesthetics in the human neonate is about 2-3 times longer than elimination in adults (Tucker and Mather, 1979). The differences in UV:MV concentration ratios for the local anesthetics proboably are due to the differences in protein binding; however, the concentration of *unbound* local anesthetic in the plasma of both mother and fetus should be the same at equilibrium (Burm, 1989).

Since the amide local anesthetics are weak bases with pK_as ranging from 7.9 to 8.2, the pH of the medium is important for the amount of dissociation and passive transfer across biological membranes (Müller-Holve et al., 1986).

The location and rate of administration of the amide local anesthetics have a pronounced effect on drug distribution and the onset of anesthesia. The onset of anesthesia may vary by as much as 15 minutes when injected into different segments of the spinal column (Data et al., 1995). Local anesthetics are injected over an extended period of time when properly administered. This gives time for the local anesthetic to recirculate, reaching an equilibrium concentration in the plasma with adequate metabolism and elimination rates to keep this equilibrium below toxic concentrations. When a local anesthetic is inadvertently mistaken for another drug and accidentally administered, it is likely to be injected rapidly since the rate of infusion is not important for some pharmaceuticals. First-pass metabolism is then very important to prevent toxic amounts of a local anesthetic from reaching vital organs and tissues. The interplay of hepatic metabolism, extrahepatic metabolism, plasma protein concentrations, blood flow characteristics and elimination will play an important part in tempering the dose.

Metabolism of the local anesthetics occurs primarily in the liver by N-dealkylation and/or hydrolysis, with subsequent hydroxylation. The amount of dealkylated and hydroxylated products vary according to species and local anesthetic administered. N-dealkylation appears to

Table 10. Mean Percentage of the Local Anesthetic Dose Excreted Unchanged and Mean Biological Half-Life in Adults and Neonates

Local Anesthetic	Mean Percentage of Dose Excreted Unchanged in the Urine		Mean Biological Half-life (hr)	
	Adults	Neonates	Adults	Neonates
Mepivacaine	3.5	43.4	1.9, 3.17	8.95, 8.69
Lidocaine	4.2	19.7	1.6, 1.8	3.05, 3.16
Bupivacaine			3.5	8.1
Etidocaine		14.6	2.6	6.42

Source: Morgan et al. (1978)

be the primary mechanism of detoxification in humans and primates, while hydroxylation is the major route of metabolism in rodents and sheep. In all species, almost all hydroxylated metabolites, and some unhydroxylated, are excreted as glucuronide and sulphate conjugates. It has been suggested that the aniline metabolites may follow a volatile pathway of excretion (e.g., lung rather than kidney) (Nickel, 1996).

There is a concern with small children and neonates that the enzyme systems that metabolize local anesthetics are not fully developed and may result in more prolonged serum concentrations of the anesthetic and its metabolites (Essink-Tebbes et al., 1999).

9.1.2.2 Bupivacaine

9.1.2.2.1 Metabolism of Bupivacaine

For detailed information on individual metabolism studies refer to **Appendix A, Table A-1, Metabolism Studies of Bupivacaine in Humans and Experimental Animals.** The proposed metabolites of bupivacaine are listed in **Table 11** and the metabolic pathway is presented in **Figure 2**. Differences in metabolites detected in the urine samples of various species are shown in **Table 12**.

Metabolism of bupivacaine occurs primarily in the liver, with urinary and biliary excretion of bupivacaine and its metabolites. The primary liver enzyme responsible for the dealkylation of bupivacaine to PPX was shown to be CYP3A4 *in vitro* using human liver microsomes, although CYP2C19 and CYP2D6 may play a minor role in the formation of PPX

(Gantenbein et al., 2000). Biliary excretion appears to be more extensive in rats than in primates (Goehl et al., 1973).

Bupivacaine is extensively metabolized in all species tested, as is evident from the small amount of unchanged bupivacaine excreted in the urine. The urinary excretion of bupivacaine is pH dependent, but the excretion of its desbutyl metabolite, PPX, is not (Friedman et al., 1982). The metabolism and metabolites of bupivacaine are similar to those of mepivacaine and ropivacaine.

Metabolism of bupivacaine in humans, and other primates, occurs primarily by N-dealkylation, followed by hydroxylation, usually of the aromatic or pipecolyl ring (Goehl et al., 1973). Dealkylation of bupivacaine gives desbutylbupivacaine (PPX). In humans, the major metabolites detected in the urine after dosing with a racemic mixture of bupivacaine were, in the order of decreasing concentration, levo and dextro enantiomers of PPX, 4'-hydroxybupivacaine, and 3'-hydroxybupivacaine (Fawcett et al., 1999). There was large variability in the rates of clearance of the enantiomers, leading the investigators to conclude that the metabolism of bupivacaine may be mediated by different amounts of microsomal enzymes such as P450 isoforms, each with different substrate stereoselectivities.

In rats, metabolism is primarily by hydroxylation, with minor amounts of dealkylated products (Caldwell et al., 1977 abstr.; Goehl et al., 1973). 3'-Hydroxybupivacaine (12.1% of the dose) and 4'-hydroxybupivacaine (7.7%) were the major metabolites seen in 24-hour urine collections from rats. Only small quantities of the dealkylated products PPX (0.3% of the dose) and pipecolic acid (1.6%) were determined in a 24-hour urine sample.

In rats and humans, a large fraction of the hydroxylated metabolites of bupivacaine are excreted as glucuronide conjugates in the urine. In rats, about 80-97.8% of 3'-hydroxy- and 4'-hydroxybupivacaine were detected as glucuronide conjugates (Goehl et al., 1973; Caldwell et al., 1978).

Only one study was found that tried to determine the concentration of 2,6-xylidine in urine after exposure to bupivacaine, and no xylidine was found (Mather et al., 1971 and unpublished data; cited by Tucker and Mather, 1979); however, the details of the study were not available. In the studies reviewed, it is often difficult to identify or assess the amount of all excreted metabolites since only derivatives of the ^{14}C- or ^{3}H-labeled pipecolyl moiety of the bupivacaine molecule were determined. In all of the studies reviewed where pipecolic acid was

detected and quantitated using a radioactive label on the pipecolyl moiety, it could be assumed that equal quantities of 2,6-xylidine were also formed as a product of the hydrolysis of PPX. However, further hydroxylation of any 2,6-xylidine may occur resulting in minor amounts of 2,6-xylidine. If this is the case, then the formation of 4-hydroxyxylidine after administration of bupivacaine may be substantial in primates and humans, but not in rats. To our knowledge, no one has tried to determine the amount of 4-hydroxyxylidine after bupivacaine administration.

The excretion of PPX into breast milk after administration of bupivacaine during delivery in mothers revealed that bupivacaine and PPX are differentially excreted into breast milk (Ortega et al., 1999). While the mean bupivacaine serum and breast milk concentrations were highest 2 hours after epidural injection (0.23 and 0.09 g/mL, respectively), the mean serum and breast milk PPX concentrations were highest 12 hours after administration (0.17 and 0.25 g/mL, respectively). The mean breast milk/serum ratio at peak concentrations was only 0.39 for bupivacaine, but 1.47 for PPX. This is an important factor when considering that the toxicity of PPX is twice that of bupivacaine (Bruguerolle et al., 1994; cited by Ortega et al, 1999).

The antiulcerative drug cimetidine, an H2-receptor agonist that is capable of impairing oxidation in the liver, has been shown to noncompetitively inhibit the metabolism of bupivacaine *in vitro* in rat hepatocytes at concentrations of 100 µg/mL (396 µM) (Thompson et al., 1987). However, cimetidine did not appear to affect the metabolism or clearance of bupivacaine significantly in *in vivo* human studies. The synergism/antagonism of cimetidine is important since it is used as an anesthetic premedication for the prevention of acid aspiration syndrome (Pihlajamaki et al., 1988).

Table 11. Bupivacaine, Its Salts, and Its Metabolites

Parent (shaded) or Metabolite Code[a]	Metabolite	Hill Formula	CASRN	Chem. Abstr. References & References Used
BUP	Bupivacaine; (±)-Bupivacaine; Marcaine; *DL*-Bupivacaine; 1-Butyl-*N*-(2,6-dimethylphenyl)-2-piperidinecarboxamide; 1-Butyl-2′,6′-pipecoloxylidide	$C_{18}H_{28}N_2O$	38396-39-3	517
BUP	Bupivacaine; (±)-Bupivacaine; Marcaine; *DL*-Bupivacaine; 1-Butyl-*N*-(2,6-dimethylphenyl)-2-piperidinecarboxamide; 1-Butyl-2′,6′-pipecoloxylidide	$C_{18}H_{28}N_2O$	2180-92-9 (replaced by 38396-39-3 ca. 1991)	1128
BUP·H$_2$CO$_3$	Bupivacaine carbonate; Bupiv-Carb	$C_{18}H_{28}N_2O@2CH_2O_3$	55750-21-5	3
(R+)-BUP	(+)-Bupivacaine; (*R*)-(+)-Bupivacaine; (*R*)-Bupivacaine; *D*-(+)-Bupivacaine; *d*-Bupivacaine	$C_{18}H_{29}ClN_2O$	27262-45-9	90
(S-)-BUP	(-)-Bupivacaine; (*S*)-(-)-Bupivacaine; (*S*)-Bupivacaine; *L*-(-)-Bupivacaine; Levobupivacaine	$C_{18}H_{29}ClN_2O$	27262-47-1	114
BUP·HCl	Bupivacaine hydrochloride	$C_{18}H_{29}ClN_2O$	18010-40-7	144
BUP·HCl	Bupivacaine hydrochloride	$C_{18}H_{29}ClN_2O$	14252-80-3	40 Irestadt et al. (1976)
PPX	2′,6′-Pipecoloxylidide [racemic]; 2′,6′-Pipecolylxylidide; PPX; *N*-Desbutylbupivacaine; Mono-*N*-demethylmepivacaine; *N*-(2,6-Dimethylphenyl)-2-piperidinecarboxamide	$C_{14}H_{20}N_2O$	15883-20-2	45 Goehl et al. (1973)
(R)-PPX	(*R*)-2′,6′-Pipecoloxylidide; (*R*)-Desbutylbupivacaine; (-)-2′,6′-Pipecoloxylidide	$C_{14}H_{20}N_2O$	27262-43-7	10 Fawcett et al. (1999) (Bupivacaine)
(S)-PPX	(*S*)-2′,6′-Pipecoloxylidide; (*S*)-Desbutylbupivacaine; (+)-2′,6′-Pipecoloxylidide; (2*S*)-*N*-(2,6-Dimethylphenyl)-2-piperidinecarboxamide	$C_{14}H_{20}N_2O$	27262-40-4	20 Fawcett et al. (1999)

Table 11. Bupivacaine, Its Salts, and Its Metabolites (Continued)

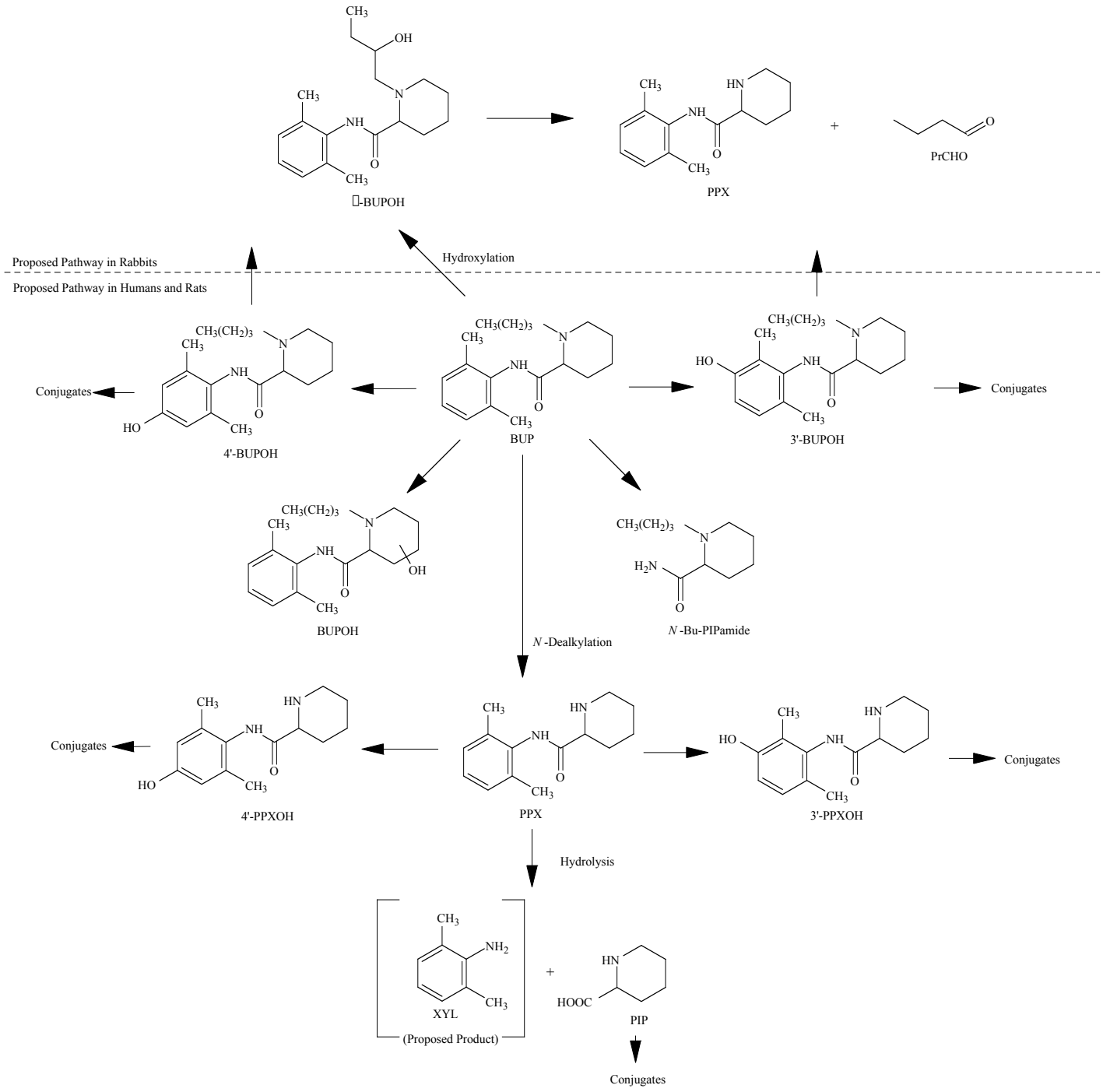
Parent (shaded) or Metabolite Code[a]	Metabolite	Hill Formula	CASRN	Chem. Abstr. References & References Used
N-Bu-PIPamide	*N*-Butylpipecolyl-2-amide; 1-Butyl-2-piperidinecarboxamide; *N*-Butylpiperidine-2-carboxylic acid amide **[Mentioned in Dennhardt et al. (1978a), Dennhardt and Konder (1980), and Dennhardt (1981) as "unexpected and unexplained." Formation of this compound would appear to require cleavage by hydrogenolysis of the C-N bond between the *m*-xylene and amino moieties of 2,6-xylidine.]**	$C_{10}H_{20}N_2O$	67810-45-1	1 Dennhardt & Konder (1980)
3´-BUPOH	3´-Hydroxybupivacaine; 1-Butyl-*N*-(3-hydroxy-2,6-dimethylphenyl)-2-piperidinecarboxamide; 1-Butyl-3´-hydroxypipecolo-2,6´-xylidide	$C_{18}H_{28}N_2O_2$	51989-46-9	10 Dennhardt & Konder al. (1980)
(R)-3´-BUPOH	(2*R*)-3´-Hydroxybupivacaine; (2*R*)-1-Butyl-*N*-(3-hydroxy-2,6-dimethylphenyl)-2-piperidinecarboxamide	$C_{18}H_{28}N_2O_2$	220604-08-0	1 Fawcett et al. (1999)
(S)-3´-BUPOH	(2*S*)-3´-Hydroxybupivacaine; (2*S*)-1-Butyl-*N*-(3-hydroxy-2,6-dimethylphenyl)-2-piperidinecarboxamide	$C_{18}H_{28}N_2O_2$	220604-03-5	1 Fawcett et al. (1999)
4´-BUPOH	4´-Hydroxybupivacaine; 1-Butyl-*N*-(4-hydroxy-2,6-dimethylphenyl)-2-piperidinecarboxamide	$C_{18}H_{28}N_2O_2$	51989-47-0	13 Dennhardt & Konder (1980)
(R)-4´-BUPOH	(2*R*)-4´-Hydroxybupivacaine; (2*R*)-1-Butyl-*N*-(4-hydroxy-2,6-dimethylphenyl)-2-piperidinecarboxamide	$C_{18}H_{28}N_2O_2$	220604-05-7	1 Fawcett et al. (1999)
(S)-4´-BUPOH	(2*S*)-4´-Hydroxybupivacaine; (2*S*)-1-Butyl-*N*-(4-hydroxy-2,6-dimethylphenyl)-2-piperidinecarboxamide	$C_{18}H_{28}N_2O_2$	220604-01-3	1 Fawcett et al. (1999)
BUPOH	Hydroxybupivacaine; 1-Butyl-*N*-(2,6-dimethylphenyl)hydroxy-2-piperidinecarboxamide [unspecified attachment for hydroxyl group]	$C_{18}H_{28}N_2O_2$	67800-43-5	1 Dennhardt et al. (1978a)

Table 11. Bupivacaine, Its Salts, and Its Metabolites (Continued)

Parent (shaded) or Metabolite Code[a]	Metabolite	Hill Formula	CASRN	Chem. Abstr. References & References Used
*-BUPOH	*N*-(2,6-Dimethylphenyl)-1-(2-hydroxybutyl)-2-piperidinecarboxamide	$C_{18}H_{28}N_2O_2$	64013-17-8	1 Bouché & Lhoest (1976)
3´-PPXOH	3´-Hydroxy-2´,6´-pipecoloxylidide [racemic]; *N*-(3-Hydroxy-2,6-dimethylphenyl)-2-piperidinecarboxamide; 3´-Hydroxydesbutylbupivacaine	$C_{14}H_{20}N_2O_2$	247061-17-2	1 Arvidsson et al. (1999)
4´-PPXOH	4´-Hydroxy-2´,6´-pipecoloxylidide [racemic]; *N*-(4-Hydroxy-2,6-dimethylphenyl)-2-piperidinecarboxamide; 4´-Hydroxydesbutylbupivacaine	$C_{14}H_{20}N_2O_2$	51989-48-1	2 Falany et al. (1999) Goehl et al. (1973)
PrCHO	Butyraldehyde; Butanal **[A probable metabolite of a proposed metabolite (Bouché & Lhoest, 1976). No link was found between this compound and bupivacaine in Chem. Abstr.]**	C_4H_8O	123-72-8	7765 Bouché & Lhoest (1976)
PIP	Pipecolic acid; *DL*-Pipecolic acid; (±)-Pipecolic acid; a-Pipecolinic acid; (*RS*)-2-Piperidinecarboxylic acid; Piperolinic acid; Homoproline; 2-Carboxypiperidine; etc.	$C_6H_{11}NO_2$	535-75-1	518 Goehl et al. (1973)
XYL	2,6-Xylidine; 2,6-Dimethylaniline **[Has not been confirmed as a bupivacaine metabolite.]**	$C_8H_{11}N$	87-62-7	[24 with CASRN linked to metabolism] **(Conjectural)**

[a] (R)- and (S)- prefixes indicate specific optically active enantiomers.
Primes on numbers in codes indicate that ring hydroxylation is on the xylidine or toluidine moiety. Primes are not used on codes for hydroxyl derivatives of xylidine and toluidine.
Numbers without primes in codes indicate that substitution is not on the xylidine or toluidine moiety (usually on the pipecolyl moiety).
The lower-case Greek letter beta in a code indicates that hydroxylation is on the C-2 of the butyl moiety.

Figure 2. Metabolic Pathway for Bupivacaine in Humans and Experimental Animals



Chiral center is located on C-2 in the pipecolyl ring.
Bracketed 2,6-xylidine has not been reported, but should be formed plus its metabolites in an amount at least equal to the amount of pipecolic acid (PIP).

Table 12. Metabolites of Bupivacaine Detected *In Vivo* and Their Amounts in Humans and Experimental Animals

Metabolite Code	Range of Mean Amounts of Bupivacaine Metabolites Detected in Urine and [Plasma][a]									
	Humans		Primates		Rabbits		Rats		Sheep[c]	
BUP	X	0.13-6%[1.45] 0.09[b]	X	5.9%			X	2.8-3.4%	X	<1.0 □M
PPX	X	1.21-5% [0.17] 0.25[b]	X	3.8%			X	0.3-1.1%	X	1.4 □M
N-Bu-PIPamide*	X	n.q.					X	n.q.		
3'-BUPOH	X	3.66%			X	n.q.	X	12.1-45.3%	X	39 □M
4'-BUPOH	X	0.09-1.71% [0.02]	X	8.0%	X	n.q.	X	7.7-28.3%		3 □M
BUPOH	X	n.q.					X	n.q.		
□-BUPOH	X	n.q.			X	n.q.				
4'-PPXOH	X	4.9%	X	4.9%					X	<3 □M
3'-PPXOH									X	6 □M
PrCHO*										
PIP			X	51.7%			X	1.6-6.0%		
XYL*										
Percent of dose in urine & time				79.9% (24-hr)				27-50% (24-hr)		
Percent of dose in feces & time				6.0% (24-hr)				28-29% (24-hr)		

* These compounds have been proposed as metabolites, but they have not been confirmed.

[a] Urinary excretion is measured as the percentage of the administered dose found in the urine and are recorded here as unbracketed numbers. The plasma concentrations (□g/mL) are recorded here in brackets.

[b] Detected in breast milk (□g/mL).

[c] Concentration of bupivacaine in sheep urine was reported as molarity only.

n.q. = not quantitated

9.1.2.2.2 Pharmacokinetic of Bupivacaine

For detailed information on individual pharmacokinetics studies, refer to **Appendix A** and **Table A-2, Pharmacokinetics Studies of Bupivacaine in Humans and Experimental Animals**.

The percentage of the dose that was bound to plasma proteins was found to be 95.2% in humans *in vivo* (Emanuelsson et al., 1995).

There are notable differences in the duration of bupivacaine persistence in plasma after different forms of administration. When bupivacaine was epidurally infused at a rate of 25 mg/hr in young healthy human adult males for 21 hours, the mean peak plasma level was 0.90 g/mL at the termination of infusion (Emanuelsson et al., 1995).

Due to the increased use of bupivacaine as an epidural anesthetic in obstetrics, there are numerous studies of the pharmacokinetics of bupivacaine in the mother, fetus, and neonate. Today, bupivacaine is most often used in epidural analgesia in combination with narcotics such as fentanyl or sufentanil (Walker, 1997). This combination provides a more rapid onset of anesthesia, more complete and longer lasting pain relief, and less motor blockade than if either drug were used alone. Concentrations of bupivacaine in the maternal plasma of 18 pregnant women peaked 10 minutes after the termination of epidural infusion (dose: ≥35 mg) with plasma concentration ranges between 91 and 430 ng/mL (mean ~200) (Caldwell et al., 1978). Bupivacaine appeared in the blood of the fetus (29 ng/mL) ten minutes after the end of infusion. The fetal venous plasma concentrations of bupivacaine reached a plateau after 75 minutes (44 ng/mL) and lasted until the end of fetal sampling at ninety minutes after epidural administration to the mother. Similar concentrations of bupivacaine in the fetus were found at 20 minutes (29 ng/mL) and 60 minutes (34 ng/mL) in another study (Caldwell et al., 1976 abstr.). The mean umbilical venous/maternal venous bupivacaine concentrations have been measured between 0.33 and 0.59 (Fernando et al., 1997; Caldwell et al., 1978; Cooper et al., 1977). In all studies reviewed involving the use of bupivacaine during delivery there was no correlation between bupivacaine use and lower Apgar scores. In one study, neonates born to 40 women that had received bupivacaine during delivery had Apgar scores above seven when measured five minutes after delivery (Fernando et al, 1997). In a study of 19 mothers and their babies, 11 neonates had eliminated all bupivacaine in plasma 24 hours after delivery and 8 had bupivacaine concentrations between 0.005 and 0.01 g/mL (Cooper et al., 1977).

The terminal phase half-life in the mother is significantly increased after epidural administration of amide local anesthetics due to the slow absorption of the drug from the epidural space into the blood stream (Morgan et al., 1978). This is of particular importance when considering fetal exposure to local anesthetics. The $T_{1/2\beta}$ has been measured as 5 minutes in pregnant mothers administered bupivacaine epidurally (Caldwell et al., 1976 abstr.) and 7.0 ± 2.4 minutes in 6 human volunteers injected i.v. (Boyes et al., 1971; cited by Scott et al., 1973). The mean $T_{1/2\beta}$ in mothers has been measured as 1.05 to 1.25 hours (63 to 75 minutes) (Caldwell et al., 1976 abstr., 1978) and 76.4 ± 55.6 minutes in 6 healthy human volunteers (Boyes et al., 1971; cited by Scott et al., 1973). Bupivacaine elimination from the blood of neonates was biphasic, with a rapid initial phase in the first two hours after birth, followed by a much slower elimination phase (mean $T_{1/2\beta}$ = 25 hours). The initial rapid elimination phase in neonates may be due to first-pass absorption into the newly matured lungs. The longer time for elimination in neonates could be attributed to either greater tissue absorption or decreased elimination (Caldwell et al., 1976 abstr., 1978).

The coadministration of epinephrine with bupivacaine results in half the plasma levels of patients receiving bupivacaine alone at the same dose (Reynolds et al., 1989).

Bupivacaine is a mixture of enantiomers levobupivacaine [(*S*)-(–)-bupivacaine] and dexbupivacaine [(*R*)-(+)-bupivacaine]. Dexbupivacaine has been determined to be more potent in its ability to block sodium channels because of its ability to bind more rapidly and more tightly than levobupivacaine (Anesthetic & Life Support Advisory Committee, 1999). The greater anesthetic potency of dexbupivacaine also results in its greater toxicity when compared to that of levobupivacaine. It has been found that the ratio of renal to total bupivacaine clearance in humans is much higher for (*R*)-(+)-bupivacaine than for (*S*)-(–)-bupivacaine (Fawcett et al., 1999).

9.1.2.3 Etidocaine

9.1.2.3.1 Metabolism of Etidocaine

For detailed information on individual metabolism studies refer to **Appendix B, Table B-1, Metabolism Studies of Etidocaine in Humans**.

Etidocaine, like the other amide local anesthetics, is extensively metabolized in the liver. Only 0.17-0.33% of the dose was recovered unchanged as etidocaine (Morgan et al., 1977b). The metabolism of etidocaine may not be as extensive in neonates since the percentage of etidocaine in neonatal blood that was excreted unchanged in the 48-hour urine collections of 8 neonates was estimated to be 14% (Morgan et al., 1978).

Extraction and analysis of a 48-hour urine collection from a healthy human volunteer resulted in the determination of eight dealkylated and hydroxylated metabolites of etidocaine (Vine et al., 1978). Quantitative analysis of the metabolites was not possible because of the methods used; however, it was estimated that these metabolites accounted for approximately 10% of the total dose of etidocaine. The metabolites of etidocaine and a diagram of the metabolic pathway for etidocaine are presented in **Table 13** and **Figure 3**, respectively. Examination of 48-hour urine samples from two patients, one dosed orally with etidocaine and the other dosed by epidural injection, resulted in the isolation of nine metabolites (Thomas et al., 1976). Two of the nine metabolites isolated metabolites were unknown. A quantitative determination of the metabolites was performed on urine collected from the patient receiving the epidural dose. Six metabolites: 2-amino-2-butyroxylidide, 2-*N*-ethylamino-2-butyroxylidide, 2,6-dimethylaniline (2,6-xylidine), and 4-hydroxy-2,6-dimethylaniline (4-hydroxyxylidine) accounted for approximately 31% of the total dose of etidocaine (see **Table 14** for individual amounts).

The concentrations of the metabolites 2,6-xylidine and its metabolite, 4-hydroxyxylidine, were determined after etidocaine administration and found to be much lower than concentrations after lidocaine administration (Morgan et al, 1977a abstr.). Xylidine and 4-hydroxyxylidine accounted for only 3.0% of the dose of etidocaine, whereas the amount of the two metabolites after lidocaine administration was 75% of the dose (Keenaghan and Boyes, 1972). The authors attributed this difference to the presence of the branched alkyl side chain in the etidocaine moiety. Sixteen N-dealkylated and hydroxylated metabolites were found in this study but were not presented in the published abstract.

The placental transfer of three metabolites of etidocaine (etidocaine, 2-*N*-propylamino-2'-butyroxylidide, and 2-*N*-ethylamino-2'-butyroxylidide) were found to be related to their hydrophobicity (Morgan et al., 1977b). The greater the lipid solubility, the greater the cord/maternal plasma ratio.

The metabolite 2-*N*-propylamino-2'-butyroxylidide was found to be more concentrated in the blood of neonates than in the blood of the mothers (Morgan et al., 1978). This pattern is also true for lidocaine and mepivacaine (Mihaly et al., 1977; Moore et al., 1975; all cited by Morgan et al., 1978).

No relationship was seen between the last dose of etidocaine to delivery and cord/maternal venous blood or plasma concentration ratios of etidocaine (Morgan et al., 1977b). 2-*N*-Propylamino-2'-butyroxylidide and 2-*N*-ethylamino-2'-butyroxylidide appeared in maternal blood at 5 minutes after dosing and in cord blood at 30 minutes post-administration. Of eight neonates born to mothers that received epidural etidocaine, three had measurable levels of 4-hydroxyxylidine and five had levels of xylidine. From 2 to 6 □g of 4-hydroxyxylidine was detected in 48-hour urine collections. The amounts of xylidine detected were between trace and 1.9 □g in the 48-hour urine of neonates. It is interesting to note that in the neonates who had excreted 4-hydroxyxylidine, no xylidine was detected, and in the ones who had excreted xylidine, no 4-hydroxyxylidine was detected.

The hydantoin metabolite 3-(2,6-dimethylphenyl)-5-ethyl-2,4-imidazolidininedione was determined to comprise 10% of the dose excreted in the urine of 2 male patients and two male volunteers (Morgan et al., 1977c). The presence of the hydantoin metabolite may contribute to the lower toxicity of etidocaine when compared to bupivacaine since hydantoins are known to have anticonvulsant properties (Scott, 1975; cited by Morgan et al., 1977c).

Table 13. Etidocaine, Its Salts, and Its Metabolites

Parent (shaded) or Metabolite Code[a]	Metabolite	Hill Formula	CASRN	Chem. Abstr. References & References Used
ETI	Etidocaine; (±)-*N*-(2,6-Dimethylphenyl)-2-(ethylpropylamino)butanamide; 2-(*N*-Ethylpropylamino)-2′,6′-butyroxylidide	$C_{17}H_{28}N_2O$	36637-18-0	226
ETI·HCl	Etidocaine hydrochloride; Duranest hydrochloride	$C_{17}H_{29}ClN_2O$	36637-19-1 (Replaced 52300-99-9)	4 (52300-99-9) 43 (36637-19-1)
EtABX	2-*N*-Ethylamino-2′-butyroxylidide; *N*-(2,6-Dimethylphenyl)-2-(ethylamino)butanamide	$C_{14}H_{22}N_2O$	59359-47-6	3 Thomas et al. (1996)
PrABX	2-*N*-Propylamino-2′-butyroxylidide; *N*-(2,6-Dimethylphenyl)-2-(propylamino)butanamide	$C_{15}H_{24}N_2O$	59359-48-7	3 Thomas et al. (1996)
ABX	2-Amino-2′-butyroxylidide; *N*-(2,6-Dimethylphenyl)-2-aminobutanamide	$C_{12}H_{18}N_2O$	59359-46-5	15 Thomas et al. (1996)
3′-ETIOH	3-Hydroxyetidocaine; *N*-(2,6-Dimethyl-3-hydroxyphenyl)-2-(*N*,*N*-ethylpropylamino)butyramide; 2-(Ethylpropylamino)-*N*-(3-hydroxy-2,6-dimethylphenyl)butanamide	$C_{17}H_{28}N_2O_2$	69754-76-3	1 Vine et al. (1978)
4′-ETIOH	4-Hydroxyetidocaine; *N*-(2,6-Dimethyl-4-hydroxyphenyl)-2-(*N*,*N*-ethylpropylamino)butyramide; 2-(Ethylpropylamino)-*N*-(4-hydroxy-2,6-dimethylphenyl)butanamide	$C_{17}H_{28}N_2O_2$	69754-72-9	1 Vine et al. (1978)
3′-EtABXOH	*N*-(3-Hydroxy-2,6-dimethylphenyl)-2-(ethylamino)butanamide; *N*-(2,6-Dimethyl-3-hydroxyphenyl)-2-(ethylamino)butanamide; 2-(Ethylamino)-*N*-(3-hydroxy-2,6-dimethylphenyl)butanamide (ditto all with "butyramide" instead of "butanamide")	$C_{14}H_{22}N_2O_2$	69754-70-7	1 Vine et al. (1978)

Table 13. Etidocaine, Its Salts, and Its Metabolites (Continued)

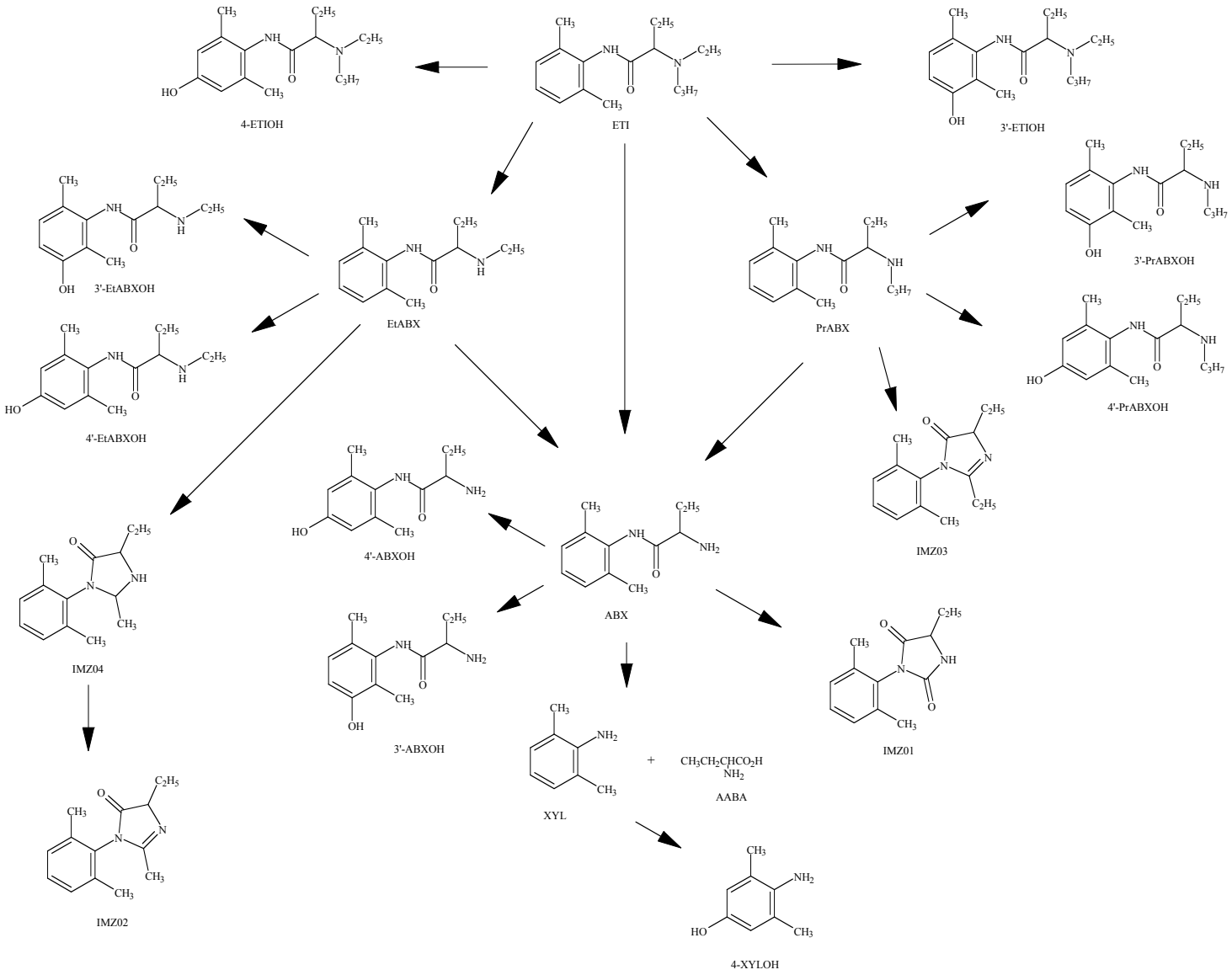
Parent (shaded) or Metabolite Code[a]	Metabolite	Hill Formula	CASRN	Chem. Abstr. References & References Used
4′-EtABXOH	*N*-(4-Hydroxy-2,6-dimethylphenyl)-2-(ethylamino)butanamide; *N*-(2,6-Dimethyl-4-hydroxyphenyl)-2-(ethylamino)butanamide; 2-(Ethylamino)-*N*-(4-hydroxy-2,6-dimethylphenyl)butanamide (ditto all with "butyramide" instead of "butanamide")	$C_{14}H_{22}N_2O_2$	69754-74-1	1 Vine et al. (1978)
3′-PrABXOH	*N*-(3-Hydroxy-2,6-dimethylphenyl)-2-(propylamino)butanamide; *N*-(2,6-Dimethyl-3-hydroxyphenyl)-2-(propylamino)butanamide (ditto all with "butyramide" instead of "butanamide")	$C_{15}H_{24}N_2O_2$	69754-75-2	1 Vine et al. (1978)
4′-PrABXOH	*N*-(4-Hydroxy-2,6-dimethylphenyl)-2-(propylamino)butanamide; *N*-(2,6-Dimethyl-4-hydroxyphenyl)-2-propylaminobutyramide	$C_{15}H_{24}N_2O_2$	69754-71-8	1 Vine et al. (1978)
3′-ABXOH	2-Amino-*N*-(3-hydroxy-2,6-xylyl)butyramide; 2-Amino-*N*-(3-hydroxy-2,6-dimethylphenyl)butanamide; *N*-(2,6-Dimethyl-3-hydroxyphenyl)-2-aminobutyramide	$C_{12}H_{18}N_2O_2$	69754-73-0	1 Vine et al. (1978)
4′-ABXOH	2-Amino-*N*-(4-hydroxy-2,6-xylyl)butyramide; 2-Amino-*N*-(4-hydroxy-2,6-dimethylphenyl)butanamide; *N*-(2,6-Dimethyl-4-hydroxyphenyl)-2-aminobutyramide	$C_{12}H_{18}N_2O_2$	69754-69-4	1 Vine et al. (1978)
IMZ01	3-(2,6-Dimethylphenyl)-5-ethyl-2,4-imidazolidinedione	$C_{13}H_{16}N_2O_2$	64226-24-0 [113800-53-6, *(R)*-] [113800-58-1 *(S)*-]	1 Morgan et al. (1977c)
IMZ02	1-(2,6-Dimethylphenyl)-2-methyl-4-ethyl-2-imidazolin-5-one; 3-(2,6-Dimethylphenyl)-5-ethyl-3,5-dihydro-2-methyl-4*H*-imidazol-4-one	$C_{14}H_{18}N_2O$	64429-46-5	1 Morgan et al. (1977c)
IMZ03	1-(2,6-Dimethylphenyl)-2,4-diethyl-2-imidazolin-5-one; 3-(2,6-Dimethylphenyl)-2,5-diethyl-3,5-dihydro-4*H*-imidazol-4-one	$C_{15}H_{20}N_2O$	64226-25-1	1 Morgan et al. (1977c)
IMZ04	3-(2,6-Dimethylphenyl)-5-ethyl-2-methyl-4-imidazolidinone	$C_{14}H_{20}N_2O$	59359-49-8	1 Thomas et al. (1976)

Table 13. Etidocaine, Its Salts, and Its Metabolites (Continued)

Parent (shaded) or Metabolite Code[a]	Metabolite	Hill Formula	CASRN	Chem. Abstr. References & References Used
AABA	□-Aminobutyric acid; 2-Aminobutanoic acid; AABA; (□)-□-Aminobutyric acid; *DL*-Aminobutyric acid; Butyrine; *DL*-Ethylglycine; Homoalanine **(Conjectural.)**	$C_4H_9NO_2$	2835-81-6 (Replaced 80-60-4)	601 (2835-81-6) 1269 (80-60-4)
XYL	2,6-Xylidine; 2,6-Dimethylaniline	$C_8H_{11}N$	87-62-7	[24 with CASRN linked to metabolism] Thomas et al. (1996) Morgan et al. (1977b)
4-XYLOH	4-Hydroxy-2,6-xylidine; 4-Amino-3,5-dimethylphenol; 4-Amino-3,5-xylenol; 4-Amino-3,5-dimethylphenol; 4-Hydroxy-2,6-dimethylaniline	$C_8H_{11}NO$	3096-70-6	75 Thomas et al. (1996) Morgan et al. (1977b)

[a] (R)- and (S)- prefixes indicate specific optically active enantiomers.
Primes on numbers in codes indicate that ring hydroxylation is on the xylidine or toluidine moiety. Primes are not used on codes for hydroxylated metabolites of xylidine and toluidine Numbers without primes in codes indicate that substitution is not on the xylidine or toluidine moiety (usually on the pipecolyl moiety).

Figure 3. Metabolic Pathway for Etidocaine in Humans



4-XYLOH may also be produced by the hydrolysis of 4'-ETIOH, 4'-EtABXOH, 4'-PrABXOH, and 4'-ABXOH as well as by hydroxylation of xylidine, but the pathways are not shown due to figure constraints.

Table 14. Identified Metabolites of Etidocaine in Man and Their Relative Amounts Detected in Human Urine Samples

Code	Compound	Percent of Dose in Human Urine	Reference(s)
ETI	2-*N*-Ethylpropylamino-2-butyroxylidide; Etidocaine	0.21%	Thomas et al. (1996)
EtABX	2-*N*-Ethylamino-2'-butyroxylidide	0.45%	Thomas et al. (1996)
PrABX	2-*N*-Propylamino-2'-butyroxylidide		Thomas et al. (1996)
ABX	2-Amino-2'-butyroxylidide	9.5%	Thomas et al. (1996)
3'-ETIOH[a]	*N*-(2,6-Dimethyl-3-hydroxyphenyl)-2-(*N*,*N*-ethylpropylamino)butyramide		Vine et al. (1978)
4'-ETIOH[a]	*N*-(2,6-Dimethyl-4-hydroxyphenyl)-2-(*N*,*N*-ethylpropylamino)butyramide		Vine et al. (1978)
3'-EtABXOH[a]	*N*-(2,6-Dimethyl-3-hydroxyphenyl)-2-(*N*-ethylamino)butyramide		Vine et al. (1978)
4'-EtABXOH[a]	*N*-(2,6-Dimethyl-4-hydroxyphenyl)-2-(*N*-ethylamino)butyramide		Vine et al. (1978)
3'-PrABXOH[a]	*N*-(2,6-Dimethyl-3-hydroxyphenyl)-2-(*N*-propylamino)butyramide		Vine et al. (1978)
4'-PrABXOH[a]	*N*-(2,6-Dimethyl-4-hydroxyphenyl)-2-(*N*-propylamino)butyramide		Vine et al. (1978)
3'-ABXOH[a]	*N*-(2,6-Dimethyl-3-hydroxyphenyl)-2-aminobutyramide		Vine et al. (1978)
4'-ABXOH[a]	*N*-(2,6-Dimethyl-4-hydroxyphenyl)-2-aminobutyramide		Vine et al. (1978)
IMZ01	3-(2,6-Dimethylphenyl)-5-ethyl-2,4-imidazolidinedione	10%	Morgan et al. (1977c)
IMZ02	1-(2,6-Dimethylphenyl)-2-methyl-4-ethyl-2-imidazolin-5-one		Morgan et al. (1977c)
IMZ03	1-(2,6-Dimethylphenyl)-2,4-diethyl-2-imidazolin-5-one		Morgan et al. (1977c)
IMZ04	2-Methyl-*N*-2,6-dimethylphenyl-5-ethyl-4-imidazolidinone		Thomas et al. (1996)
AABA	□-Aminobutyric acid; 2-Aminobutanoic acid		
XYL	2,6-Dimethylaniline; 2,6-Xylidine	0.46-2.16%	Thomas et al. (1996) Morgan et al. (1977b)
4-XYLOH	4-Hydroxy-2,6-dimethylaniline; 4-Hydroxyxylidine	3.23-8.3%	Thomas et al. (1996) Morgan et al. (1977b)

[a] These metabolites were quantified in human urine and found together to comprise 10% of the administered dose.

9.1.2.3.2 Pharmacokinetics of Etidocaine

For detailed information on individual pharmacokinetics studies refer to **Appendix B, Table B-2, Pharmacokinetics Studies of Etidocaine in Humans and Experimental Animals**.

In five human male and female patients undergoing routine surgery, the protein-bound fraction of etidocaine in the blood was 93.4% to 94.8% (Morgan et al., 1977b). The *in vitro* protein binding of etidocaine is much lower in pregnant women during delivery (73.6%) than it is in pregnant women in week 35-37 of gestation (94.4%). The lower protein binding is probably due to the lower hematocrit in pregnant women (0.36) and also the fact that almost all of the etidocaine in the blood is confined to the plasma (Diem and Lentner, 1971; Assali and Brinkman, 1972; Kurata and Wilkinson, 1974; all cited by Morgan et al., 1977b). This may have important implications for fetal transfer since it is the unbound fraction of etidocaine in maternal blood that is available for transport across the placenta. The hematocrit in umbilical cord blood at delivery has been measured as 0.47, which is the same as the hematocrit in a healthy adult male (Diem and Lentner, 1971; cited by Morgan et al., 1977b; Morgan et al., 1978). This higher concentration of plasma proteins in fetal blood when compared to maternal blood may help offset the lower amount of plasma protein binding in the fetus. There was a large interpatient variation in the cord/maternal whole blood concentration ratio of etidocaine (range 0.161 to 1.38), but the cord/maternal plasma concentration ratio was less variable (range 0.234 to 0.546).

The elimination half-life of etidocaine in blood after i.v. and epidural administration was reported to be 2.6 and 6.5 to 7.7 hours , respectively (Tucker and Mather, 1975; cited by Morgan et al., 1977b). The mean elimination half-life of etidocaine in the plasma of pregnant (5.10 ± 2.58) and nonpregnant (5.46 ± 1.04) women was not found to be significantly different; however, the range of the half-life of etidocaine in plasma was significantly greater in pregnant women than in nonpregnant subjects (Morgan et al., 1977b). The mean half-life of elimination of etidocaine in neonates taken from urinary data was reported to be 6.42 hours (Morgan et al., 1978).

The mean blood/plasma ratio of etidocaine in fetal umbilical blood (1.24 ± 0.64) was much higher than seen in male and nonpregnant female adults (0.55 ± 0.03 and 0.64 ± 0.08, respectively) (Morgan et al, 1977b; Morgan et al., 1978). This indicates that even if total fetal/maternal blood concentrations of etidocaine are at equilibrium, more etidocaine may be unbound and available for absorption in the fetus. There was no significant difference observed

in the elimination of etidocaine in pregnant women (14.0 ± 3.5 mL/min/kg) when compared to that of nonpregnant women (14.6 ± 4.6 mL/min/kg).

In sheep, the $t_{1/2\beta}$ and $t_{1/2\beta}$ in the neonate and the nonpregant adult are very similar after i.v. administration of 2.5 mg/kg; however, due to the larger volume of distribution in the neonate (4.64 L/kg) when compared to that of the nonpregnant adult (1.52 L/kg), total body clearance and hepatic clearance were almost three times as much in the neonate as was seen in the nonpregnant adult sheep (Pedersen et al., 1982).

9.1.2.4 Lidocaine

9.1.2.4.1 Metabolism of Lidocaine

For detailed information on individual metabolism studies refer to **Appendix C, Table C-1, Metabolism Studies of Lidocaine in Humans and Experimental Animals**.

The metabolism of lidocaine is the most studied of all the amide local anesthetics and much information is available for interspecies comparison. The metabolism of lidocaine occurs primarily in the liver; however, extrahepatic metabolism of lidocaine has been detected *in vitro* and *in vivo* (Akerman et al., 1966). The deethylation of lidocaine to monoethylglycinexylidide (MEGX) has been shown to be mediated by cytochrome P450 isoenzyme CYP3A4 in transfected HepG2 cells and up to 60% of this deethylase activity could be inhibited by CYP3A4 antibodies in human microsomes (Bargetzi et al., 1989; Imaoka et al., 1990; both cited by Reichel et al., 1998). In rats, MEGX formation was attributed to CYP2C11 and CYP2B1 P450 isozymes. Lidocaine had no specificity for cytochrome P-448 as predicted by molecular geometrics (Parke et al., 1988). The metabolites of lidocaine as well as the metabolic pathway are presented in **Table 15** and **Figure 4**, respectively.

Lidocaine shows pronounced interspecies variability in its metabolism (Keenaghan and Boyes, 1972). **Table 16** presents data on the urinary excretion of lidocaine metabolites in various species after oral administration. Biliary excretion of reabsorbed metabolites from the intestinal tract was evident in the rat; however, biliary excretion of lidocaine and its metabolites is not as important in humans. The half-life of lidocaine disappearance was estimated to be less than 30 minutes in rats, as compared to a half-life of 45 to 60 minutes in dogs and 90 minutes in man. The primary route of metabolism in the rat was via hydroxylation. It has been shown that the metabolism of lidocaine in the rat may vary depending on age (Fujita et al., 1985; cited by

Coutts et al., 1987). The primary route of metabolism in man was by hydrolysis of the amide bond in lidocaine or one of its dealkylated metabolites with subsequent hydroxylation. It has been shown that dogs and rabbits can metabolize 2,6-xylidine to 2-amino-3-methylbenzoic acid (Short et al., 1989; Kammerer and Schmitz, 1986) and that the guinea pig may also be able to produce this metabolite from lidocaine; however it has not been detected in man (Keenaghan and Boyes, 1972). Humans appear to preferentially hydroxylate the aromatic ring of lidocaine at the 4-carbon while rats preferentially hydroxylate at the 3-carbon (Coutts et al., 1987; Keenaghan and Boyes, 1972).

The aromatic metabolite of lidocaine, 2,6-xylidine, is not a major metabolite excreted in the urine of man; however, its hydroxylated derivative, 4-hydroxyxylidine, is the predominant metabolite determined in urine and in the plasma. Xylidine can be formed from either lidocaine or its metabolite MEGX *in vitro* (Parker et al., 1996). It is thought that lidocaine may be hydroxylated prior to amide hydrolysis, resulting in little formation of xylidine but formation of large amounts of 4'-hydroxyxylidine (Tam et al., 1987). The percentage of the lidocaine dose (oral dose of 250 mg or ~3.125 mg/kg bw) excreted as 2,6-xylidine in the 24-urine collection from 20 healthy human volunteers was 1.0% of the dose, but 4-hydroxyxylidine comprised 72.6 percent of the dose. After two i.v. bolus doses of 100 mg each of lidocaine hydrochloride followed immediately by i.v. infusion at a rate of 3 mg/min for 48 hours in two patients, the 72-hour urine of one patient contained predominantly 4-hydroxyxylidine (80.1% of the lidocaine dose). Xylidine was not detected in the urine of either patient (<0.2 µg/mL) (Tam et al, 1987). Xylidine was not detected in the plasma; however, the concentration of 4-hydroxyxylidine in plasma was even greater than the concentration of lidocaine itself immediately after i.v. infusion (4.5 and 2.8 µg/mL, respectively) and 10 hours after infusion (1.7 and 1.0 µg/mL, respectively). Following epidural administration in four patients, as much as 75% of the dose of lidocaine was recovered as 2,6-xylidine and 4-hydroxyxylidine (Morgan et al., 1977a). All of the *in vivo* animal studies reviewed showed that xylidine was not a major metabolite in any species except guinea pigs, which excreted 16.2% of the dose as xylidine in 24-hour urine collections (Keenaghan and Boyes, 1972). Because 4-hydroxyxylidine has been shown to cause mutations in Salmonella, the toxicity of this metabolite should not be overlooked (Beardsley, 1994). Lidocaine been shown to undergo intrachannel hydrolysis (78% of the time with lidocaine) in a

bovine AChE preparation using circular dichroism which was correlated with paresthesia in humans (Nickel, 1994 abstr.).

In vitro tests using human liver slices showed that the concentrations of MEGX and xylidine were similar after incubation with lidocaine (Parker et al., 1996). When liver microsomes, S9 fractions, and liver homogenates were used, relatively higher concentrations of MEGX and relatively lower concentrations of xylidine than those seen *in vivo* were determined (Parker et al., 1996).

N-Hydroxyamides are of importance since some have been shown to be carcinogenic (e.g., *N*-hydroxy-2-acetylaminofluorene). It has been proposed that *N*-hydroxylidocaine and *N*-hydroxymonoethylglycinexylidide could be possible metabolites of lidocaine (Mather and Thomas, 1972; cited by Nelson et al., 1978). This was based on the fact that treatment of urine samples with $TiCl_3$ after lidocaine administration resulted in an increase of lidocaine and monoethylglycinexylidide when compared to untreated samples, and when urine was acidified the amount of metabolites increased suggesting oxidation at the amide nitrogen instead of the more basic amino group. However, after oral treatment with lidocaine (250 mg), no *N*-hydroxylidocaine or *N*-hydroxymonoethylglycine-xylidide was detected in human urine (Nelson et al., 1974). In another study, no *N*-hydroxylidocaine or *N*-hydroxymonoethylglycinexylidide was found in human urine after oral lidocaine administration to two subjects or after i.v. infusion of lidocaine for treatment of arrhythmia (Nelson et al., 1978).

An N-hydroxylated xylidine derivative, *N*-hydroxyxylidine, a known xylidine metabolite, forms adducts with hemoglobin (Bryant et al., 1994). This has been detected in the hemoglobin of tobacco smokers and nonsmokers (Bryant et al., 1988; cited by Bryant et al., 1994). Lidocaine has been known to induce methemoglobinemia, which may be severe in some patients (Bryant et al., 1994). The amount of xylidine-hemoglobin adducts formed after treatment with lidocaine correlates with the amount of the metabolite *N*-hydroxylidine. In nine patients receiving treatment for cardiac arrhythmia, concentrations of xylidine-hemoglobin adducts ranged from approximately 110 to 690 ng 2,6-xylidine/g hemoglobin and increases above the initial baseline concentrations ranged from 93 to 636 ng/g hemoglobin. Two patients had measurable baseline concentrations of xylidine-hemoglobin adducts prior to lidocaine treatment. One patient had an adduct concentration between 50 and 100 ng 2,6-xylidine/g hemoglobin and the other had a concentration of 423 ng 2,6-xylidine/g hemoglobin. In rats administered

lidocaine and xylidine on separate occasions, 0.84% (788 g/g hemoglobin) of the xylidine dose was bound to hemoglobin and 0.027% (1.8 g xylidine/g hemoglobin) of the lidocaine dose was detected as hemoglobin adducts. *N*-Hydroxylidine was primarily formed from the oxidation of xylidine and not from the hydrolysis of *N*-hydroxylidocaine or *N*-hydroxymonoethylglycinexylidide, which were not found in this study. *N*-Hydroxyxylidine was estimated to be approximately 1% of the administered dose excreted in human urine after oral administration of lidocaine hydrochloride to two subjects (Nelson et al., 1978).

The lidocaine metabolite monoethylglycinexylidide (MEGX) is at least 80% as toxic as lidocaine and contains antiarrythmic properties itself (Miyabe et al., 1998; Kakiuchi et al., 1999). In cardiac patients treated with lidocaine for more than one day (Drayer et al., 1983 abstr.), serum concentrations were readjusted for protein binding and it was determined that the plasma MEGX/lidocaine ratio was 0.68 ± 0.49. GX was very low (ratio not provided). GX plasma concentration normalized to the rate of infusion of lidocaine decreased with age. It was determined that MEGX plays a greater role in the pharmacokinetics of lidocaine than GX. The metabolites MEGX and GX accumulated over time in the myocardium of dogs and humans with no time-dependent delay (Handel et al., 1982 abstr.)

In infants and children (aged 3 months to 4 years) administered lidocaine i.v. (5 mg/kg bolus, followed by infusion with 2.5 mg/kg/hr), plasma levels of lidocaine increased linearly from 2.5 g/mL at the initiation of infusion to less than 3 g/mL at 5 hours, while MEGX concentrations were 0.1 g/mL at initiation of infusion to 2.5 g/mL 5 hours later (Miyabe et al., 1998).

There is evidence of the metabolism of lidocaine in the fetus and neonate (Kuhnert et al., 1979). In a study of 25 pregnant women and their offspring it was found that lidocaine concentrations in maternal plasma were higher than concentrations in cord plasma, but the concentrations of metabolites (MEGX and GX) were equal to or greater than the concentration of metabolites in maternal plasma. MEGX was detected 10 minutes after the first lidocaine dose and GX was detected 40 minutes after the first lidocaine dose in maternal plasma. GX was found in some cord samples when it was not detectable in maternal plasma. Lidocaine, MEGX, and GX were detected in the urine of the neonates for up to three days after delivery. The urinary excretion of lidocaine in the mother was about

In cirrhotic patients dosed orally, peak plasma concentrations of lidocaine were more than twice the amount of control concentrations in healthy subjects and MEGX concentrations were about 70% of control concentrations (Munoz et al., 1999). In orally dosed patients with hepatitis, peak plasma concentrations of lidocaine were comparable to those of controls and MEGX concentrations were more than 20% higher than control concentrations. The half-life of lidocaine absorption was much longer in patients with liver cirrhosis and hepatitis when compared to that of controls. The mean level of MEGX measured in another group of patients with liver dysfunction was about 27 µmol/L at 30 minutes and about 30 µmol/L one hour after i.v. administration.

Human liver slices from five donors produced xylidine in a 4-hour study when incubated *in vitro* with MEGX or LID (Parker et al., 1996). No xylidine was detected when liver homogenates, human liver microsomes, or S9 fractions were incubated with MEGX or lidocaine. It is suggested that the enzyme primarily responsible for the hydrolysis of lidocaine may be labile in subcellular fractions.

Extrahepatic formation of MEGX after lidocaine hydrochloride injection was demonstrated in an anhepatic patient awaiting a liver transplant (Sallie et al., 1992). It has been further shown *in vitro* that extrahepatic metabolism in rats may occur in the kidney and lung, but not the brain (Tanaka et al., 1994). A very slow rate of MEGX and 3-hydroxylidocaine formation (0.022-0.024 nmol/min/mg protein) was observed in rat kidney microsomes as well as a slow rate of formation of MEGX (0.87 nmol/min/mg). The rate of formation of MEGX and 3-hydroxylidocaine by rat hepatic microsomes was 4.84 and 0.64 nmol/min/mg, respectively. There is evidence that CYP2B1 may be the sole isoenzyme responsible for the de-ethylation of lidocaine in rat pulmonary and renal microsomes.

Lidocaine *N*-oxide has been proposed as a metabolite of lidocaine in humans, but has not been recovered in any *in vivo* metabolism studies reviewed. It was found *in vitro* using NADPH-supplemented rat liver microsomes (Patterson et al., 1986).

Several imidazolidinones have been proposed as metabolites of lidocaine, but only one has been detected in the blood. The mean peak concentration of N^1-ethyl-2-methyl-N^3-(2,6-dimethylphenyl)-4-imidazolidinone (0.08 g/mL) in the plasma of two male human subjects occurred 30 minutes after lidocaine administration (Nelson et al., 1977). The other subject in this study had no detectable concentrations of N^1-ethyl-2-methyl-N^3-(2,6-dimethylphenyl)-4-

imidazolidinone. The mean concentration of N^1-ethyl-2-methyl-N^3-(2,6-dimethylphenyl)-4-imidazolidinone had decreased to 0.035 g/mL in the two subjects 180 minutes after administration.

The 3- and 4-hydroxylated metabolites of lidocaine were not glucuronide conjugates but may be sulfate conjugated (Thomas and Meffin, 1972).

Table 15. Lidocaine, Its Salts, and Its Metabolites

Parent (shaded) or Metabolite Code[a]	Metabolite	Hill Formula	CASRN	CASRN SORT	Chem. Abstr. References & References Used
LID	Lidocaine; Xylocaine; Lignocaine; 2-(Diethylamino)-2′,6′-acetoxylidide; a-Diethylamino-2,6-acetoxylidide	$C_{14}H_{22}N_2O$	137-58-6	137586	5176
LID·H_2CO_3	Lidocaine carbonate	$C_{14}H_{22}N_2O_2CH_2O_3$	56934-02-2	56934022	4
LID·H_2SO_4	Lidocaine sulfate	$C_{14}H_{24}N_2O_5$	24847-67-4	24847674	3
LID·HCl	Lidocaine hydrochloride	$C_{14}H_{23}ClN_2O$	73-78-9	73789	929
LID·HCl·H_2O	Lidocaine hydrochloride monohydrate	$C_{14}H_{25}ClN_2O_2$	6108-05-0	6108050	6
MEGX	MEGX; Monoethylglycinexylidide; Monoethylglycylxylidide; *N*-(2,6-Dimethylphenyl)-2-(ethylamino)acetamide; 2-(Ethylamino)-2′,6′-acetoxylidide; *N*-(*N*-Ethylglycyl)-2,6-xylidide; EGX; L 86; Deethyllidocaine; *N*,*N*-Ethylglycinexylidide; □-Ethylamino-2′,6′-dimethylacetanilide	$C_{12}H_{18}N_2O$	7728-40-7	7728407	209 Keenaghan & Boyes (1972)
GX	Glycine xylidide; Glycyl xylidide; *N*-Glycyl-2,6-xylidine; GX; 2-Amino-2′,6′-acetoxylidide; □-Amino-2,6-dimethylacetanilide; 2-Amino-2′,6′-dimethylacetanilide	$C_{10}H_{14}N_2O$	18865-38-8	18865388	106 Keenaghan & Boyes (1972)
3′-LIDOH	3-Hydroxylidocaine; 2-(Diethylamino)-*N*-(3-hydroxy-2,6-dimethylphenyl)acetamide	$C_{14}H_{22}N_2O_2$	34604-55-2	34604552	46 Keenaghan & Boyes (1972)
4′-LIDOH	4-Hydroxylidocaine; 2-(Diethylamino)-*N*-(4-hydroxy-2,6-dimethylphenyl)acetamide	$C_{14}H_{22}N_2O_2$	39942-41-1	39942411	8 Keenaghan & Boyes (1972)
□-LIDOH	Hydroxymethyllidocaine; 2-(Diethylamino)-*N*-[2-(hydroxymethyl)-6-methylphenyl)acetamide	$C_{14}H_{22}N_2O_2$	64585-18-8	64585188	12 Tanaka et al. (1994) Carrier et al. (1993)

Table 15. Lidocaine, Its Salts, and Its Metabolites (Continued)

Parent (shaded) or Metabolite Code[a]	Metabolite	Hill Formula	CASRN	CASRN SORT	Chem. Abstr. References & References Used
LID-N-Ox	Lidocaine *N*-oxide; 2-(Diethyloxidoamino)-*N*-(2,6-dimethylphenyl)acetamide; 2-(Diethylamino)-*N*-(2,6-dimethylphenyl)acetamide N^2-oxide; 2-(Diethylamino)-2′,6′-xylidide **[Rat liver microsomes supplemented with NADPH metabolized lidocaine to the *N*-oxide (Patterson et al., 1986). No other studies were identified that found this compound as a lidocaine metabolite.]**	$C_{14}H_{22}N_2O_2$	2903-45-9	2903459	7 Patterson et al. (1986)
	N-Hydroxylidocaine **[Synthesized by Nelson et al. (1977, 1978) as a potential metabolite, but did not match any metabolites.]**	$C_{14}H_{22}N_2O_2$	52662-13-2	52662143	3 Nelson et al. (1974, 1977, 1978)
3′-MEGXOH	3-Hydroxy-*N*-(*N*-ethylglycyl)-2,6-xylidine; 2-(Ethylamino)-*N*-(3-hydroxy-2,6-dimethylphenyl)acetamide; 3′-Hydroxy-MEGX	$C_{12}H_{18}N_2O_2$	34604-56-3	34604563	20 Tam et al. (1987)
4′-MEGXOH	*p*-Hydroxy-□-ethylamino-2,6-dimethylacetanilide; 2-(Ethylamino)-*N*-(4-hydroxy-2,6-dimethylphenyl)acetamide; 4′-Hydroxy-MEGX	$C_{12}H_{18}N_2O_2$	64585-10-0	64585100	5 Tam et al. (1987)
	N-Hydroxy-MEGX; □-(Ethylamino)-2,6-dimethylphenylacetohydroxamic acid; *N*-(2,6-Dimethylphenyl)-2-(ethylamino)-*N*-hydroxyacetamide **[Synthesized by Nelson et al. (1977) as a potential metabolite, but did not match any metabolites.]**	$C_{12}H_{18}N_2O_2$	52662-14-3	52662143	2 Nelson et al. (1974, 1977)
3′-GXOH	3-Hydroxy-*N*-glycyl-2,6-xylidine; 2-Amino-*N*-(3-hydroxy-2,6-dimethylphenyl)acetamide; 3′-Hydroxy-GX	$C_{10}H_{14}N_2O_2$	112606-87-8	112606878	1 Coutts et al. (1987)
4′-GXOH	4-Hydroxy-*N*-glycyl-2,6-xylidine; 2-Amino-*N*-(4-hydroxy-2,6-dimethylphenyl)acetamide; 4′-Hydroxy-GX	$C_{10}H_{14}N_2O_2$	108966-35-4	108966354	2 Tam et al. (1987)

Table 15. Lidocaine, Its Salts, and Its Metabolites (Continued)

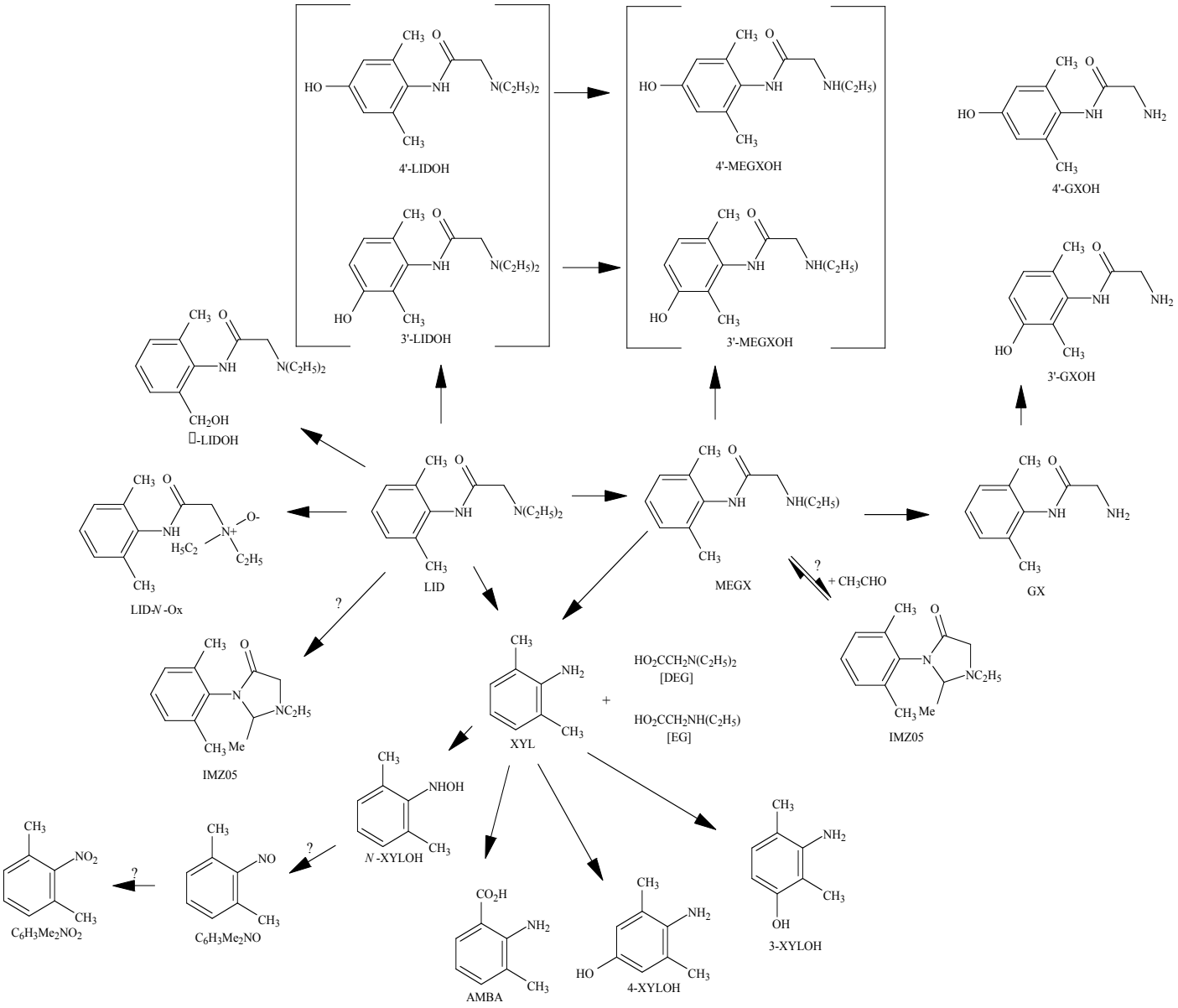
Parent (shaded) or Metabolite Code[a]	Metabolite	Hill Formula	CASRN	CASRN SORT	Chem. Abstr. References & References Used
IMZ05	N^1-Ethyl-2-methyl-N^3-(2,6-dimethylphenyl)-4-imidazolidinone; 3-(2,6-Dimethylphenyl)-1-ethyl-2-methyl-4-imidazolidinone; 1-Ethyl-2-methyl-3-(2,6-xylyl)-4-imidazolidinone **[Probable source MEGX plus acetaldehyde source (e.g., ethanol) *in vivo* (established in Rhesus monkeys) or MEGX plus acetaldehyde in urine or acetaldehyde contaminant in solvents. Might also arise through intramolecular condensation of lidocaine (Breck and Trager, 1971; Nelson et al., 1973; Carrier et al., 1993).]**	$C_{14}H_{20}N_2O$	32845-42-4	32845424	3 Breck & Trager (1971) Nelson et al. (1977) Carrier et al. (1993)
IMZ06	3-(2,6-Dimethylphenyl)-1,2-diethyl-4-imidazolidinone **[Formed by lidocaine oxidation by biomimetic systems (Carrier et al., 1993).]**	$C_{15}H_{22}N_2O$	152361-30-3	152361303	1 Carrier et al. (1993)
IMZ07	3-(2,6-Dimethylphenyl)-1-ethyl-4-imidazolidinone **[Possible formation from MEGX and endogenous or contaminant formaldehyde (Nelson et al., 1973).]**	$C_{13}H_{18}N_2O$	51044-98-5	51044985	1 Nelson et al. (1973)
XYL	2,6-Xylidine; 2,6-Dimethylaniline	$C_8H_{11}N$	87-62-7	87627	[24 with CASRN linked to metabolism] Keenaghan & Boyes (1972)
DEG	*N*,*N*-Diethylglycine; (Diethylamino)acetic acid	$C_6H_{13}NO_2$	1606-01-5	1606015	63 Nelson et al. (1977)
EG	*N*-Ethylglycine; (Ethylamino)acetic acid	$C_4H_9NO_2$	627-01-0	627010	47
3-XYLOH	3-Hydroxy-2,6-xylidine; 3-Amino-2,4-dimethylphenol	$C_8H_{11}NO$	100445-96-3	100445963	4 Coutts et al. (1987)

Table 15. Lidocaine, Its Salts, and Its Metabolites (Continued)

Parent (shaded) or Metabolite Code[a]	Metabolite	Hill Formula	CASRN	CASRN SORT	Chem. Abstr. References & References Used
4-XYLOH	4-Hydroxy-2,6-xylidine; 4-Amino-3,5-dimethylphenol	$C_8H_{11}NO$	3096-70-6	3096706	75 Tam et al. (1987)
AMBA	2-Amino-3-methylbenzoic acid; 2-Amino-*m*-toluic acid; 3-Methyl-2-aminobenzoic acid; 3-Methylanthranilic acid	$C_8H_9NO_2$	4389-45-1	4389451	141 Kammerer & Schmitz (1986)
N-XYLOH	*N*-Hydroxy-2,6-xylidine; 2,6-Dimethylphenylhydroxylamine	$C_{14}H_{22}N_2O_2$	3096-63-7	3096637	0 [See Nelson et al. (1977, 1978).]
$C_6H_3Me_2NO$	1,3-Dimethyl-2-nitrosobenzene; 2-Nitroso-*m*-xylene; 2,6-Dimethylnitrosobenzene **[Possible metabolite, but no evidence (Kammerer and Schmitz (1986).]**	C_8H_9NO	19519-71-2	19519712	18 Kammerer & Schmitz (1986)
$C_6H_3Me_2NO_2$	1,3-Dimethyl-2-nitrobenzene; 2-Nitro-*m*-xylene; 2,6-Dimethylnitrobenzene; 2-Nitro-1,3-dimethylbenzene; 2-Nitro-1,3-xylene **[Possible metabolite, but no evidence (Kammerer and Schmitz (1986).]**	$C_8H_9NO_2$	81-20-9	81209	190 Kammerer & Schmitz (1986)

[a] Primes on numbers in codes indicate that ring hydroxylation is on the xylidine or toluidine moiety. Primes are not used on codes for hydroxylated metabolites of xylidine and toluidine.
Numbers without primes in codes indicate that substitution is not on the xylidine or toluidine moiety (usually on the pipecolyl moiety).
The lower-case Greek letter alpha in a code indicates that hydroxylation is on a xylidine methyl group.

Figure 4. Proposed Metabolic Pathway for Lidocaine in Humans and Experimental Animals



Question marks indicate pathways that have been suggested by IR spectral analysis only.

Table 16. Metabolites of Lidocaine Detected *In Vivo* and Their Amounts in Human Urine and [Plasma]

Metabolite Code	Range of Mean Amounts of Lidocaine Metabolites Detected in Urine and [Plasma][a]							
	Humans		Dogs		Guinea Pig		Rats	
LID	X	2.1-4.76%	X	2.0%	X	0.5%	X	0.2%
MEGX	X	1.7-12.68%	X	2.3%	X	14.9%	X	0.7%
GX	X	0.55-2.3%	X	12.6%	X	3.3%	X	2.1%
3'-LIDOH	X	0.1-1.3%	X	6.7%	X	0.5%	X	6.0-31.2%
4'-LIDOH	X	0.1-0.28%					X	3-5%
□-LIDOH[b]								
N-XYLOH	X	1.0%						
LID-*N*-Ox[d]								
3'-MEGXOH	X	0.04-0.3%	X	3.1%	X	2.0%	X	Minute-36.9%
4'-MEGXOH	X	0.06%						
3'-GXOH							X	Appreciable amounts
4'-GXOH	X	0.24%						
EG	X	n.q.						
DEG	X	35%						
IMZ05	X	[0.04-0.08]						
AMBA[c]								
$C_6H_3Me_2NO$[d]								
$C_6H_3Me_2NO_2$[d]								
XYL	X	0.84-1.0%	X	1.6%	X	16.2%	X	1.5%
3-XYLOH							X	Trace amounts
4-XYLOH	X	60.5-80.1%	X	25.2%	X	16.4%	X	Minor quantities 12.4%
Percent of dose in urine & time		50% (72-hr); 69.07-88.9% (24-hr)						
Percent of dose in feces & time								

[a] Urinary excretion is measured as the percentage of the administered dose found in the urine and the plasma concentrations are measured in micrograms per milliliter.
[b] Only detected *in vitro* using rat liver microsomes (Tanaka et al., 1994).
[c] Only detected *in vitro* using rabbit liver homogenates (Kammerer and Schmitz, 1986).
[d] Proposed as possible metabolites but were not detected (Kammerer and Schmitz, 1986).

9.1.2.4.2 Pharmacokinetics of Lidocaine

For detailed information on individual pharmacokinetics studies, refer to **Appendix C, Table C-2, Pharmacokinetics Studies of Lidocaine in Humans and Experimental Animals**.

Lidocaine's use is favored because of its low incidence of side effects, especially cardiovascular toxicity (Berlin-Wahlen et al., 1977). Lidocaine is used extensively as an i.v. anti-arrhythmic agent. Lidocaine is not an effective oral treatment for arrhythmia due to its low oral availability and short elimination half-life. The vasodilatory effect of lidocaine cannot be overlooked when discussing pharmacokinetics. The vasodilatory effect contributes to lidocaine's rapid onset of action when compared to the other local anesthetics and also causes its short analgesic effect.

The plasma protein-bound concentration of lidocaine was determined to be 51% (Williams et al., 1976). Protein binding of lidocaine (44%) is reduced during viral hepatitis. It was proposed in one study that protein-bound lidocaine can enter the liver and that protein-bound lidocaine may enter peripheral tissues via a "free intermediate mechanism" (Pardridge et al., 1983).

The venous/arterial blood concentration ratio of lidocaine (0.73) is higher than that of prilocaine (0.47) and this may contribute to the greater toxicity of lidocaine when compared to prilocaine (Eriksson, 1966).

Lidocaine may remain at the site of topical application for prolonged periods of time, depending on the location, being slowly released into the bloodstream and resulting in a longer half-life than after i.v. administration . When 250 mg was applied to the forearm of human volunteers, mean lidocaine concentrations peaked (~9 ng/mL) 24 hours after dermal application and lidocaine persisted in plasma for over 32 hours (Dal Bo et al., 1999). However, there was a wide deviation (1-28 hours) in the time to peak concentration. The peak plasma concentration of lidocaine after application of a lidocaine patch to the gingiva of human volunteers ranged from 16.5 to 27.2 ng/mL, 29-45 minutes after application (Noven Pharmaceuticals, 1997). Peak plasma concentrations after application of lidocaine ointment (location not provided) was 9 times higher than with the patch. In studies with EMLA cream, which contains lidocaine (2.5%) base, it was shown that the site of application can greatly affect plasma concentrations and the elimination half-life of lidocaine (Juhlin et al., 1989).

After topical application of the patch to the gingiva, elimination half-lives were similar to half-lives seen after i.v. administration of lidocaine (Noven Pharmaceuticals, 1997).

Lidocaine had a much higher affinity for accumulation in the heart than bupivacaine in rabbits, contributing to lidocaine's affect on the heart (Hollmén et al., 1973).

The umbilical vein/maternal vein concentration ratio of lidocaine after i.v. administration in a pregnant mother was 0.51, which was similar to ratios between 0.48 and 0.69 obtained in other placental transfer studies (Banzai et al., 1995). The transfer of lidocaine across the placenta by passive diffusion is rapid with equilibrium also being reached rapidly. Lidocaine does not accumulate in the amniotic fluid; however, amniotic fluid concentrations of lidocaine were found to be higher than concentrations in fetal plasma.

When lidocaine (30%) is used for male circumcision in infants, mean peak plasma concentrations are 0.27 ± 19 □g/mL (Weatherstone et al., 1993; cited by Woodman, 1999).

Certain conditions have been shown to affect the pharmacokinetics of lidocaine. Since rapid metabolism of the local anesthetics is important for detoxification, any illness that affects the liver will result in increased plasma concentrations of lidocaine and reduced amounts of metabolites.

Cerebrospinal fluid concentrations of lidocaine have been measured at 75% of plasma concentrations after i.v. administration (Glazer and Portenoy, 1991).

9.1.2.5 Mepivacaine

9.1.2.5.1 Metabolism of Mepivacaine

For detailed information on individual metabolism studies, refer to **Appendix D, Table D-1, Metabolism Studies of Mepivacaine in Humans and Experimental Animals**.

The metabolism of mepivacaine, like that of the other local anesthetics, is extensive. The urinary excretion of unchanged drug after adminstration of mepivacaine was usually very low (trace amounts to 1.6%); however, one study found concentrations of mepivacaine in four healthy male volunteers that represented 16% of the dose in acidified (pH=5.0) 24-hour urine samples (Thomas and Meffin, 1972; Reynolds, 1971). Although the excretion of mepivacaine in the urine was found to be pH-dependent, the excretion of its metabolites was determined to be pH-independent (Meffin et al., 1973b). The metabolites of mepivacaine are excreted primarily as glucuronide conjugates in the urine of rats and man (76-85% and 99%, respectively) (Hansson et al., 1965; Meffin et al., 1973b). The biliary excretion of mepivacaine is significantly higher in rats than in man (Hansson et al., 1965; Ryrfeldt and Hansson, 1971; Meffin and Thomas, 1973). As much as 51-56% of the dose in rats was excreted in the bile within 6 hours of administration (mostly hydroxylated mepivacaine), while no hydroxylated mepivacaine was found in the bile of a human female subject. The mepivacaine excreted in bile is probably reabsorbed into the blood stream from the digestive tract due to the low concentration of metabolites found in the feces. The metabolites of mepivacaine and metabolic pathway are presented in **Table 17** and **Figure 5**, respectively.

In studies with rats, 55-60% of the dose was excreted in the urine after 24 hours and 59.1-68.1% of the dose was excreted in the urine during the following 48 hours (Thomas and Meffin, 1972; Hansson et al., 1965). The feces from rats contained between 4.3 and 15.6% of the mepivacaine dose. In mice, the respired CO_2 was found to contain between 10.5 and 11.4% of the dose (Hansson et al., 1965).

In rats, the predominant metabolite found in the urine is 3'-hydroxymepivacaine (~60%) (Thomas and Meffin, 1972). Little or no 4'-hydroxymepivacaine was found in the rat. This is in contrast to the almost equal excretion of both 3'-hydroxy- and 4'-hydroxymepivacaine in the urine of human subjects. The presence of hydroxylated mepivacaine in the 24-hour urine of rats (~60% of the mepivacaine dose) is greater than that seen in the urine of humans (18-35% of the dose) (Meffin and Thomas, 1973).

Mepivacaine, like bupivacaine and ropivacaine, contains an alkylated pipecolyl moiety whose dealkylation results in the formation of pipecoloxylidide (PPX) as a metabolic product. In humans, between 1.0 and 1.2% of the dose of mepivacaine has been found as PPX in the 24-hour urine collections (Thomas and Meffin, 1972; Reynolds, 1971). This concentration is equal to or lower than concentrations of PPX found in the urine after bupivacaine administration (Lindberg et al., 1986; Pihlajamäki et al., 1990; Reynolds, 1971; Goehl et al., 1973). No plasma PPX concentrations were determined in any of the studies reviewed.

The tissue distribution of mepivacaine and its metabolites was determined in mice after i.v. injection (Kristerson et al., 1965). It was found that mepivacaine, but not its metabolites, enters the brain. Liver and kidney extracts revealed rapid metabolism as was evident from less lipid-soluble metabolites. Sixty minutes after injection, the amount of metabolites were 10 times as high as that of mepivacaine in the kidney. Four metabolites were detected, but were not quantitated. The submaxillary glands contained metabolic products equal to 0.3% of the radioactive mepivacaine dose twenty minutes after i.v. injection, but had decreased to 0.1% sixty minutes after injection.

In mice it was found that 10.5-11.4% of the ^{14}C-labeled mepivacaine dose is exhaled in the expired CO_2 (Hansson et al., 1965).

No studies were found that attempted to determine the presence of 2,6-xylidine or its derivatives in urine or plasma after mepivacaine administration. The fate of more than 50% of the dose of mepivacaine in humans is yet undetermined.

Table 17. Mepivacaine, Its Salts, and Its Metabolites

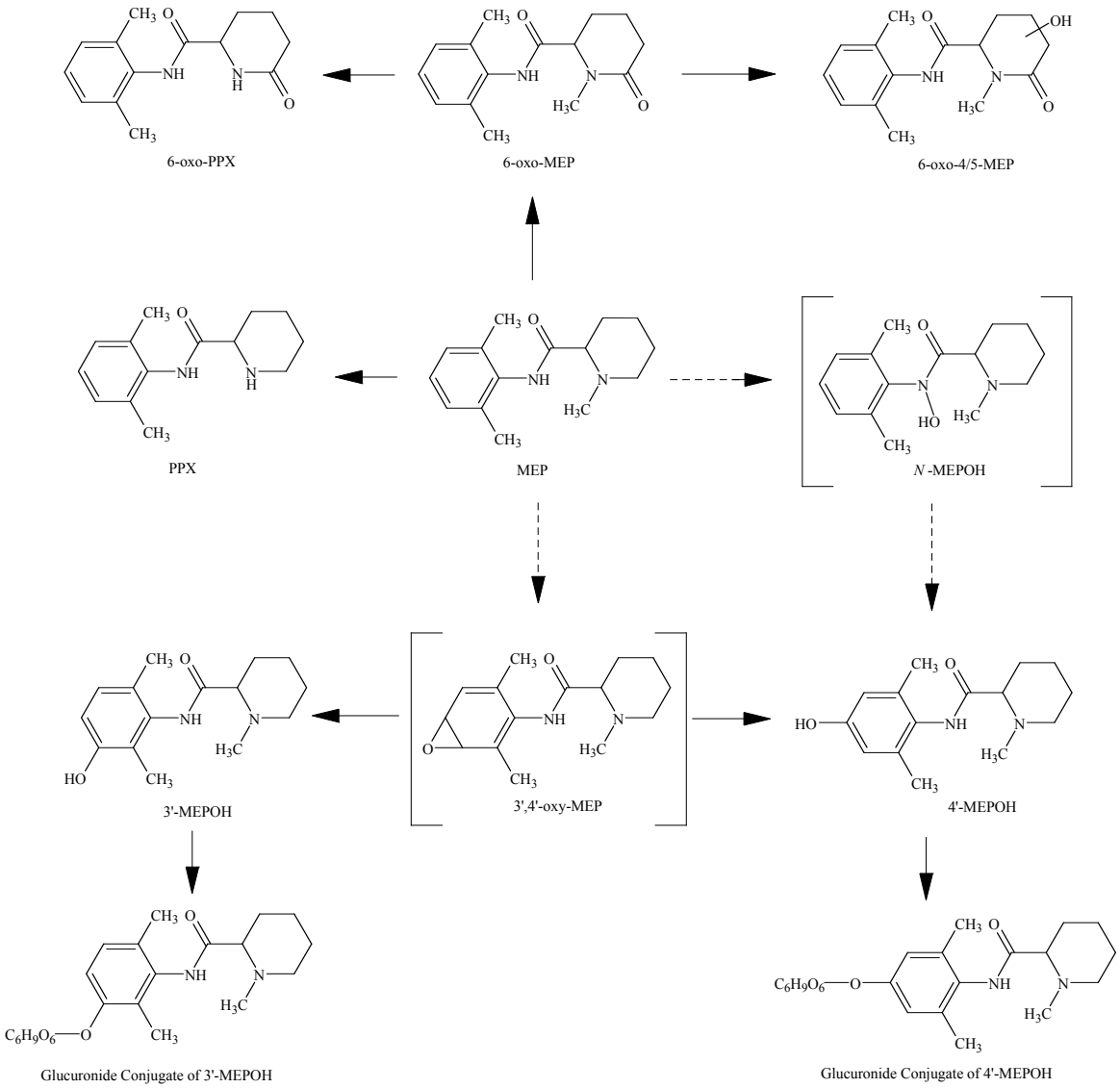
Parent (shaded) or Metabolite Code[a]	Metabolite	Hill Formula	CASRN	Chem. Abstr. References & References Used
MEP	Mepivacaine; (±)-Mepivacaine; *DL*-Mepivacaine; Carbocaine; 1-Methyl-2′,6′-pipecoloxylidide; *N*-(2,6-Dimethylphenyl)-1-methyl-2-piperidinecarboxamide	$C_{15}H_{22}N_2O$	96-88-8	547
MEP·HCl	Mepivacaine hydrochloride; Carbocaine hydrochloride; Scandonest	$C_{15}H_{22}N_2O$•HCl	1722-62-9	107
PPX	2′,6′-Pipecoloxylidide [racemic]; 2′,6′-Pipecolylxylidide; PPX; *N*-Desbutylbupivacaine; Mono-*N*-demethylmepivacaine; *N*-(2,6-Dimethylphenyl)-2-piperidinecarboxamide	$C_{14}H_{20}N_2O$	15883-20-2	45 Hansson et al. (1965)
3′,4′-oxy-MEP	1-Methylpipecolo-3′,4′-dihydro-3′,4′-epoxy-2′,6′-xylidide; 1-Methylpipecolo-3′,4′-dihydro-3′,4′-oxy-2′,6′-xylidide	$C_{15}H_{22}N_2O_2$	Not identified	Meffin and Thomas (1973)
N-MEPOH	1-Methylpipecolo-*N*-hydroxy-2′,6′-xylidide; *N*-Hydroxymepivacaine **[Authors suggested possible rearrangement of the N-hydroxy group to the 4′-position. CAS did not index the abstract for this compound.]**	$C_{15}H_{22}N_2O_2$	Not identified	Meffin and Thomas (1973)
3′-MEPOH	3′-Hydroxymepivacaine; *N*-(3-Hydroxy-2,6-dimethylphenyl)-1-methyl-2-piperidinecarboxamide; 3′-Hydroxy-1-methyl-2′,6′-pipecoloxylidide; 1-Methylpipecolo-3′-hydroxy-2′,6′-xylidide **[Major mepivacaine metabolite in horses (Harkins, 1999)]**	$C_{15}H_{22}N_2O_2$	37055-90-6	4 Harkins (1999) Meffin & Thomas (1973) Meffin et al. (1973a)
4′-MEPOH	4′-Hydroxymepivacaine; *N*-(4-Hydroxy-2,6-dimethylphenyl)-1-methyl-2-piperidinecarboxamide; 4′-Hydroxy-1-methyl-2′,6′-pipecoloxylidide; 1-Methylpipecolo-4′-hydroxy-2′,6′-xylidide	$C_{15}H_{22}N_2O_2$	616-66-0	4 Meffin & Thomas (1973) Meffin et al. (1973a)
6-oxo-MEP	*N*-(2,6-Dimethylphenyl)-1-methyl-6-oxo-1-piperidinecarboxamide; 1-Methyl-6-oxo-2′,6′-pipecoloxylidide; 1-Methyl-6-oxopipecolo-2′,6′-xylidide	$C_{15}H_{20}N_2O_2$	43063-89-4	1 Meffin et al. (1973b)
6-oxo-PPX	*N*-(2,6-Dimethylphenyl)-6-oxo-2-pyridinecarboxamide; 6-Oxopipecolo-2′,6′-xylidide; 6-Oxopipecolo-2′,6′-xylide	$C_{14}H_{18}N_2O_2$	43063-88-3	1 Meffin et al. (1973b)

Table 17. Mepivacaine, Its Salts, and Its Metabolites (Continued)

Parent (shaded) or Metabolite Code[a]	Metabolite	Hill Formula	CASRN	Chem. Abstr. References & References Used
6-oxo-4/5-MEPOH	*N*-(2,6-Dimethylphenyl)hydroxy-1-methyl-6-oxo-2-piperidinecarboxamide; Hydroxy-1-methyl-6-oxo-2′,6′-pipecoloxylidide; Hydroxy-1-methyl-6-oxopipecolo-2′,6′-xylidide **[The author presumed a hydroxy group was on position 4 or 5 of the 6-oxo-2-piperidinecarboxamide ring.]**	$C_{15}H_{20}N_2O_3$	50306-98-4	1 Meffin et al. (1973b)
	N-(2,6-Dimethylphenyl)-1-(hydroxymethyl)-6-oxo-2-pyridinecarboxamide; 1-Hydroxymethyl-6-oxo-2′,6′-pipecoloxylidide **[Examination of the original article (Meffin et al., 1973) provided no evidence for this compound. Apparently, the CASRN assignment was an indexing mistake for the abstract Chem. Abstr. 80:10211.]**	$C_{15}H_{20}N_2O_3$	43063-90-7	1 [Chemical Abstracts Service attributed to Meffin et al. (1973b).]

[a] Primes on numbers in codes indicate that ring hydroxylation is on the xylidine or toluidine moiety. Primes are not used on codes for hydroxylated metabolites of xylidine and toluidine. Numbers without primes in codes indicate that substitution is not on the xylidine or toluidine moiety (usually on the pipecolyl moiety).

Figure 5. Metabolic Pathway for Mepivacaine in Humans and Experimental Animals



* Proposed intermediates

Table 18. Metabolites of Mepivacaine Detected *In Vivo* and Their Amounts in Human Urine and [Plasma]

Metabolite Code	Range of Mean Amounts of Mepivacaine Metabolites Detected in Urine and [Plasma][a]			
	Humans		Rats	
MEP	X	<5% [3.8-5.50 g/mL]		
PPX	X	1.0-1.2% [0.20-0.38 g/mL]		
3'-MEPOH	X	9.9-17%	X	50.0-59.2%
4'-MEPOH	X	7.6-12.5%	X	n.d.
6-oxo-MEP	X	These three were found to represent not more than 10% of the administered dose of mepivacaine in a 12-hour urine sample.		
6-oxo-4/5-MEP	X			
6-oxo-PPX	X			
3',4'-oxy-MEP[b]				
N-MEPOH[b]				

[a] Urinary excretion is measured as the percentage of the administered dose found in the urine and the plasma concentrations are measured in micrograms per milliliter.
[b] These are proposed intermediates, but were not detected (Meffin and Thomas, 1973).
n.d. = not detected (Thomas and Meffin, 1972)

9.1.2.5.2 Pharmacokinetics of Mepivacaine

For detailed information on individual pharmacokinetics studies refer to **Appendix D, Table D-1, Pharmacokinetics Studies of Mepivacaine in Humans and Experimental Animals**.

Mepivacaine is a mixture of (S)- and (R)-enantiomers. The median (*S*)-mepivacaine concentration in the blood of 150 pregnant mothers given 50 mL of 1% mepivacaine was 1.18 g/mL without epinephrine and 0.86 g/mL with epinephrine immediately after birth (Schierup et al., 1988). The median (*S*)-mepivacaine concentrations in umbilical venous blood of mothers with and without epinephrine were 0.42 g/mL and 0.37 g/mL, respectively.

In a study of five healthy male volunteers, mean plasma concentrations of mepivacaine after i.v. infusion of mepivacaine hydrochloride (250 mg) was 3.5 g/mL 10 minutes after adminstration and 1.0 g/mL after 4 hours (Arthur et al., 1979).

The mean total body clearance of mepivacaine in five healthy male volunteers was 0.70 L/min and the terminal half-life was 125 min (Arthur et al., 1979). These data were similar to data provided by Tucker and Mather (1975), who calculated a terminal half-life of 114 minutes and a clearance of 0.78 L/min.

In a study of 12 pregnant women administered between 200 to 400 mg mepivacaine in a single injection and their fetuses, the mean maternal plasma concentrations were 4.47 g/mL in the 400-mg-dose group and 1.86 g/mL in the 200-mg-dose group (Teramo and Rajamaki, 1971). The fetuses of women dosed with 300-400 mg mepivacaine experienced a decrease in plasma pH (mean of –0.115). Six fetuses (5 in the 400-mg-dose group and one whose mother received 300 mg) experienced bradycardia. The mean plasma mepivacaine concentration in the fetuses that experienced bradycardia was 3.07 g/mL. The mean plasma mepivacaine concentration in the fetuses that did not experience bradycardia was 1.52 g/mL. The mean maximum mepivacaine concentration in the six fetuses that experienced bradycardia was 3.07 g/mL. One fetus had a mepivacaine concentration of 8.3 µg/mL 12 min after block with 300 mg mepivacaine, while the corresponding maternal concentration was was 2.2 µg/mL. The fetal pH in this fetus was 7.20 at about 10 minutes. No signs of toxicity were evident in the mother. A correlation exists between the severity of bradycardia and the extent of the decrease in fetal pH after paracervical block (Teramo, 1969; cited by Teramo and Rajamäki, 1971). In nonpregnant female adult and neonatal rats injected with mepivacaine hydrochloride at a dose of 25 or 50 mg/kg body weight, blood and brain concentrations of mepivacaine were higher in neonates than in adult rats; but the blood-to-brain ratios were not significantly different (Gans et al., 1980). For example, in the adult group dosed with 25 mg/kg body weight, blood and brain concentrations were 2.61 ± 0.30 g/g and 5.16 ± 0.54 g/g, respectively, 15 minutes after administration. While blood and brain concentrations of mepivacaine in neonates, also dosed with 25 mg mepivacaine /kg body weight, were 8.76 ± 1.5 g/g and 15.50 ± 2.2 g/g, respectively, 15 minutes after administration. The adult and neonatal blood-to-brain ratios in the 25-mg/kg-dose groups were 2.58 ± 0.39 and 2.01 ± 0.26, respectively.

During obstetric blocks, mepivacaine may be used with epinephrine to achieve a longer and more intense anesthesia; however, a prolongation of the second stage of labor was found in one study and may increase the risk of fetal acidosis (Zador et al., 1974; cited by Schierup et al. 1988).

The accumulation of radiolabeled mepivacaine (labeled on the pipecoloyl *N*-methyl) in tissues of mice was studied after i.v. and s.c. administration (Kristerson et al., 1965). The tissues with the highest concentration 5 and 20 minutes following administration were the brain, salivary glands, liver, kidney, bone marrow, and gastric and intestinal mucosa. One or more hours after injection, the highest concentrations of radioactivity were found in the excretory organs, such as kidney, urinary bladder, liver, and gall bladder. Radioactivity was taken up more rapidly in the brain (2-5 minutes post-administration), but also cleared more quickly than any other tissue. After 1 hour, the brain concentration was equal to that of the blood. The rapid decrease in concentrations of mepivacaine in the liver and the high activity in the gastrointestinal tract was probably due to biliary excretion. Four hours after injection, most of the radioactivity was present in the intestinal contents. Twenty-four hours after administration, most radiation was found in the intestinal tract and urinary bladder. Absorption to the tissue after s.c. administration was much slower than after i.v. administration. The distribution 20 and 60 minutes after s.c. injection was similar to that 5 minutes after i.v. administration; however, most of the radioactivity was still at the site of s.c. injection. Four hours after s.c. administration, the highest concentrations were found in the intestinal contents and the kidney.

The possibility of monitoring mepivacaine concentrations in the blood by determining saliva concentrations was studied in 29 female Sprague-Dawley rats (Gans et al., 1980). When mepivacaine was administered for 30 minutes (1 mg/mL; 1 mL/min), saliva and blood concentrations of mepivacaine were 4.79 ± 0.84 □g/g and 8.57 ± 1.07 □g/g, respectively. When mepivacaine was administered for 45 minutes (1 mg/mL; 1 mL/min), saliva and blood concentrations of mepivacaine were 14.30 ± 4.64 □g/g and 8.10 ± 0.85 □g/g, respectively. There was no clear relationship between plasma and saliva concentrations of mepivacaine; however, the accumulation of mepivacaine in the saliva over time was evident.

9.1.2.6 Prilocaine

9.1.2.6.1 Metabolism of Prilocaine

For detailed information on individual metabolism studies refer to **Appendix E, Table E-1, Metabolism Studies of Prilocaine in Humans and Experimental Animals**.

The metabolites of prilocaine as well as metabolic pathway in humans is presented in **Table 19** and **Figure 6**, respectively. The metabolism of prilocaine *in vitro* was primarily due to the hydrolysis of the amide bond (Akerman et al., 1966). The structure of prilocaine differs slightly from the other amide local anesthetics in this report due to the presence of a toluidine moiety (only one ortho-methyl group), rather than a xylidine moiety, and the unbranched alkyl chain on the amine group. Prilocaine metabolizes to *o*-toluidine instead of xylidine upon hydrolysis of the amide bound. The hydrolysis of prilocaine to *o*-toluidine is thought to proceed more readily than the hydrolysis of 2,6-xylidine after lidocaine administration due to less steric hindrance (one ortho-vs. two ortho-methyl groups) (Geddes, 1965, 1967). Even though hydrolysis is the primary means of metabolizing prilocaine, subsequent hydroxylation of *o*-toluidine and hydroxylation of prilocaine results in the greater formation of hydroxylated derivatives, similar to what is observed with xylidine after lidocaine administration (Åkerman et al., 1966; Hjelm et al., 1962). The *in vivo* metabolism of prilocaine in rats or *in vitro* metabolism using mouse liver slices was not affected by pre-treatment with SKF 525, a microsomal enzyme inhibitor shown to affect the dealkylation of *N*-alkylamines (Axelrod et al., 1954; cited by Åkerman et al., 1966; Hargreaves, 1968). This is in contrast to significant inhibition of MEGX formation from lidocaine *in vitro* after pretreatment of liver homogenates and slices from several species (Åkerman et al., 1966).

In humans, the primary metabolite excreted in 24-hour urine samples is *p*-hydroxytoluidine (34.2% of the dose), followed by *o*-hydroxytoluidine (2.7%), and *o*-toluidine (0.75%) (Hjelm et al., 1972). The hydroxylated metabolites are probably excreted almost entirely as conjugates since only 0.08% of the excreted *p*-hydroxytoluidine was unconjugated.

In a female rat, 23% of the radioactive dose of ^{14}C-labeled prilocaine was excreted in the urine and 5% was recovered in expired air in a 54-hour collection period (Geddes et al, 1965 and 1967).

The formation of methemoglobin in serum after prilocaine administration has been correlated with the concentration of its metabolite o-toluidine. Methemoglobin is formed when

ferrous iron (Fe^{2+}) in the blood is converted to ferric iron (Fe^{3+}), which reduces the blood's ability to transport oxygen to tissues. Methemoglobin concentrations are kept low (2%) in adults and children by enzymatic reduction (metHb reductase or cytochrome b5 reductase) coupled with NADH (Nilsson et al., 1990; Conroy et al., 1993; Hjelt et al., 1995; all cited by Brisman et al., 1998). Another pathway utilizes NADPH reductase, whose reaction rate is increased by methylene blue, which is used to treat methemoglobinemia. One study observed peak concentrations of *o*-toluidine (243 ng/mL) and prilocaine (632 ng/mL) 30 minutes after i.v. administration of prilocaine plus lidocaine (both 25 mg) in six full-term male newborn piglets (Klein et al., 1994). Topical application of EMLA cream to the penile area of the piglets resulted in a peak plasma concentration of 39 ng/mL prilocaine at 30 minutes post-application, and no formation of *o*-toluidine. In piglets dosed both i.v. (25 mg of lidocaine and 25 mg prilocaine) and topically with 1 g of EMLA cream, methemoglobin concentrations were 0.9-3.0% in the i.v. group and 0.7-2.0% in the topically dosed group (Taddio et al., 1994 abstr.). In preterm neonates that received 0.5 g EMLA cream for heel lances, methemoglobin concentrations were not much different from baseline (0.2-1.1% and 0.1-0.7%, respectively) and plasma *o*-toluidine was below the limit of detection (0.025 mg/L) (Essink-Tebbes et al., 1999).

One study correlated the serum concentration of methemoglobin with the plasma concentration of *p*-hydroxytoluidine (Hjelm et al. 1972). When the plasma concentration of *p*-hydroxytoluidine was 4 □g/mL in 4 out of 5 healthy volunteers, concentrations of methemoglobin were between 10 and 15%. Methemoglobin concentration peaked 1 hour after the peak in plasma concentration of *p*-hydroxytoluidine.

The use of EMLA (2.5% lidocaine, 2.5% prilocaine) cream in neonates is not recommended and use in adults should be monitored because of the risk of methemoglobinemia following the administration of prilocaine (Brisman et al., 1998). The enzymes that reduce methemoglobin are not fully developed in neonates until 3 months of age (Nilsson et al., 1990; Tse et al., 1995; Jackobson and Nilsson, 1985; all cited by Brisman et al., 1998). In studies of the use of EMLA cream in neonates, concentrations of methemoglobin in plasma were always within safe limits (<5%) (Essink-Tjebbes, 1999; Brisman et al., 1998). Methemoglobin concentrations of 5-6% have been detected in other studies after the administration of EMLA cream but were considered to be within safe limits (Brisman et al, 1998).

The rate of methemoglobin formation was more rapid after administration of (*D*)-(□)-prilocaine than with (*L*)-(+)-prilocaine *in vivo* in cats and *in vitro* (Åkerman and Ross, 1970). The rate of *o*-toluidine formation after the administration of the racemic mixture in cats was between that of the two isomers. Peak methemoglobin concentrations after administration of (*D*)-(□)-prilocaine, (*L*)-(+)-prilocaine, and (*DL*)-(±)-prilocaine were approximately 14.5, 12, and 10%, respectively.

Prilocaine has been shown to undergo intrachannel hydrolysis (40% of the time) to *o*-toluidine in a bovine AChE preparation using circular dichroism which was correlated with paresthesia in humans (Nickel, 1994 abstr.).

The *in vitro* hydrolysis of prilocaine in several animal species was due solely to constituents of the microsomal fraction; no hydrolytic activity was seen in the soluble fraction of liver homogenates, with a higher selectivity for (*D*)-(□)-prilocaine (Åkerman and Ross, 1970). Rabbit liver homogenates appeared to have the greatest metabolic activity for prilocaine, as well as lidocaine, followed by guinea pig, mouse, rat, and cat liver homogenates.

The evidence for extrahepatic metabolism of prilocaine in humans and animals is based on pharmacokinetics and *in vitro* studies. The rate of prilocaine clearance (2.84 L/min) is much higher than the calculated hepatic blood flow rate (1.7 L/min). Results of *in vitro* studies indicate extrahepatic metabolism (Arthur et al., 1979; Åkerman et al., 1966; Geng et al., 1995; van der Meer et al., 1999). Metabolism of prilocaine occurred in lung and kidney homogenates of cats, but not from kidney and lung homogenates of rabbits (Åkerman et al., 1966). It is unlikely that the lungs are the site of extrahepatic metabolism in humans (van der Meer et al., 1999).

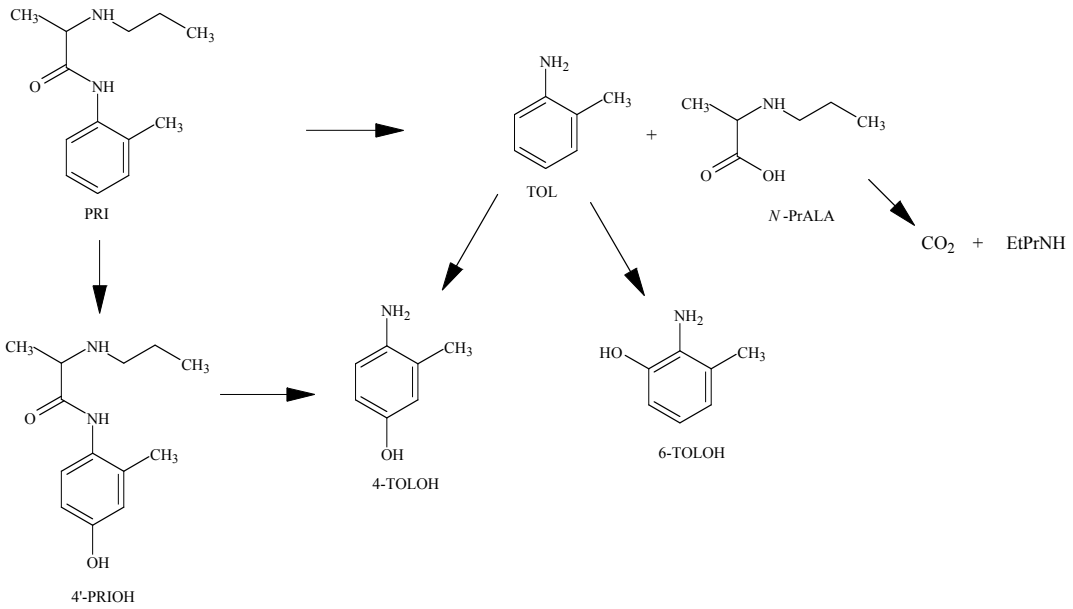
Metabolism of prilocaine should result in the formation of *N*-*n*-propylalanine in man (Geddes, 1965). *N*-*n*-Propylalanine has been determined *in vitro* with rat liver slices (Åkerman et al., 1966).

Table 19. Prilocaine, Its Salts, and Its Metabolites

Parent (shaded) or Metabolite Code[a]	Metabolite	Hill Formula	CASRN	Chem. Abstr. References & References Used
PRI	Prilocaine; *DL*-(±)-Prilocaine; Citanest; *N*-(2-Methylphenyl)-2-(propylamino)propanamide; *o*-Methyl-2-propylaminopropionanilide; 2-Methyl-□-propylaminopropionanilide; □-Propylamino-2-methylpropionanilide	$C_{13}H_{20}N_2O$	721-50-6	391
(+)-PRI	*L*-(+)-Prilocaine; (+)-Prilocaine; (*S*)-Prilocaine; (2*S*)-*N*-(2-Methylphenyl)-2-(propylamino)propanamide; *L*-(+)-2-(Propylamino)-*o*-propionotoluidide;	$C_{13}H_{20}N_2O$	14289-31-7	20
(-)-PRI	*D*-(-)-Prilocaine; (-)-Prilocaine; (*R*)-Prilocaine; (2*R*)-*N*-(2-Methylphenyl)-2-(propylamino)propanamide; *D*-(-)-2-(Propylamino)-*o*-propionotoluidide	$C_{13}H_{20}N_2O$	14289-32-8	21
PRI·HCl	Prilocaine hydrochloride; Xylonest	$C_{13}H_{21}ClN_2O$	1786-81-8	75
4′-PRIOH	*p*-Hydroxyprilocaine; 4-Hydroxyprilocaine	$C_{13}H_{21}N_2O_2$	Not identified	Hjelm et al. (1972)
TOL	*o*-Toluidine; 2-Methylaniline; 2-Methylbenzeneamine; *o*-Tolylamine; 1-Amino-2-methylbenzene [Potential metabolites, including hydroxylamine and nitroso derivatives, and their CASRNs are listed in the EMICBACK records for Gupta et al. (1987, 1989).]	C_7H_9N	95-53-4	4739
6-TOLOH	*o*-Hydroxytoluidine; 6-Hydroxy-*o*-toluidine; 2-Amino-3-methylphenol; 3-Methyl-2-aminophenol; 2-Amino-*m*-cresol; 6-Hydroxy-2-methylaniline	C_7H_9NO	2835-97-4	44 Hjelm et al. (1972)
4-TOLOH	*p*-Hydroxytoluidine; 4-Hydroxy-*o*-toluidine; 4-Amino-3-methylphenol; 4-Amino-*m*-cresol; 4-Hydroxy-2-methylaniline	C_7H_9NO	2835-99-6	326 Hjelm et al. (1972)
N-PrALA	*N*-*n*-Propylalanine; *N*-Propyl-*L*-alanine	$C_6H_{13}NO_2$	13013-28-0	3 Geddes (1965, 1967)

[a] (R)- and (S)- prefixes indicate specific optically active enantiomers.
Primes on numbers in codes indicate that ring hydroxylation is on the xylidine or toluidine moiety. Primes are not used on codes for hydroxylated derivatives of xylidine and toluidine. Numbers without primes in codes indicate that substitution is not on the xylidine or toluidine moiety (usually on the pipecolyl moiety).

Figure 6. Metabolic Pathway for Prilocaine in Humans



9.1.2.6.2 Pharmacokinetics of Prilocaine

For detailed information on individual pharmacokinetics studies refer to **Appendix E, Table E-2, Pharmacokinetics Studies of Prilocaine in Humans and Experimental Animals**.

Prilocaine, like the other amide local anesthetics in this report, except for ropivacaine, is a racemic mixture. After separate i.v. injections of 2.0% solutions of equal amounts of (*D*)-(□)-prilocaine and (*L*)-(+)-prilocaine into cats, the concentration of (*D*)-(□)-prilocaine (peak: ~9.5 □g at 5 min) was lower than that of (*L*)-(+)-prilocaine (peak: ~15.5 at 10 min) during the entire 80-minute test period (Åkerman and Ross, 1970). In rabbits, the enantiomers and racemate of prilocaine did not exhibit any significant difference in toxicity (LD_{50}); however, the cumulative anesthetic effect of (*L*)-(+)-prilocaine was more pronounced than that of (*D*)-(□)-prilocaine after repeated slow i.v. injections every 15 minutes (Åkerman and Ross, 1970). At infusion rates of 0.12 and 0.30 mg/min of 2.0% solutions, (*D*)-(□)-prilocaine was significantly less toxic than (*L*)-(+)-prilocaine, but when infused with 0.72 mg/min there was no significant difference between toxicity of the enantiomers. In 10 healthy human male volunteers, the unbound fraction of (*D*)-(□)-prilocaine in plasma was lower than the fraction of (*L*)-(+)-prilocaine (van der Meer et al., 1999). The total plasma clearance of (*D*)-(□)-prilocaine (2.57 ± 0.46 L/min) was greater than

that of (*L*)-(+)-prilocaine (1.91 ± 0.30 L/min), and the terminal half-lives of elimination were 87 ± 27 minutes and 124 ± 64 minutes, respectively. Because prilocaine is administered as a single injection due to the risk of methemoglobinemia, the importance of the enantioselectivity in the pharmacokinetics of prilocaine are probably small.

Like lidocaine, prilocaine is extensively used as a topical local anesthetic. The hydrophobicity of prilocaine may enhance its anesthetic quality by allowing more prilocaine to remain at the topical site of application for an extended period of time (Woodman et al., 1999). The pharmacokinetics of prilocaine is often compared to that of lidocaine. When prilocaine is administered with lidocaine in EMLA (2.5% lidocaine, 2.5% prilocaine) preparations, the pharmacokinetics of both drugs must be considered. In this section, the pharmacokinetics of prilocaine administered alone will be presented first, followed by the pharmacokinetics of lidocaine and prilocaine administered as EMLA.

9.1.2.6.2.1 Prilocaine

The urinary excretion of prilocaine in humans was found to be dependent on urinary pH; the lower the pH, the greater the rate of diffusion into the urine (Erikson, 1966).

After i.v. injection of prilocaine (50 mg) in five healthy male volunteers, the mean peak plasma concentration of prilocaine was 2.0 μg/mL ten minutes after administration and decreased to <0.1 μg/mL two hours after administration (Arthur et al., 1979). The mean total body clearance of prilocaine was 2.84 L/min and the terminal elimination half-life was 93 min.

When ^{14}C-labeled prilocaine was injected i.v. in near-term pregnant rats, the whole-body radiograms and scintillation counting revealed that the distribution of prilocaine was similar to the distribution of lidocaine except that the concentration of prilocaine was higher in all tissues (Katz, 1969). The highest concentrations were found in the kidney, liver, lung, heart, bowel wall, bone marrow, brain, and salivary glands. This distribution is similar to that seen in rats with peak concentrations of radioactivity occurring in the lungs (37.0 μg prilocaine/g tissue) 10 minutes after administration of prilocaine, and kidney (28.0 μg/g), spleen (19.3 μg/g), brain (18.1 μg), heart (10.9 μg/g), and liver (7.3 μg/g) 30 minutes after dosing (Åkerman et al., 1966). The concentrations of prilocaine in the placenta and fetus were higher than in maternal blood with maternal blood/fetal and maternal blood/placenta ratios of 0.31 and 0.26, respectively. The

placenta/fetus ratios of prilocaine were constant throughout the test period, indicating early equilibrium of prilocaine in the fetus, which does not vary with maternal blood concentrations.

9.1.2.6.2.2 EMLA

In a recent study, topical application of EMLA cream (1 mL) was found to be more therapeutic than application of 30% lidocaine cream for male circumcision (Woodman, 1999). In addition, the plasma concentrations of lidocaine and prilocaine were 7.5 times lower than with 30% lidocaine. When 0.5 g EMLA was applied topically to a 5-cm^2 area of the heel in 25 human neonates for 30 minutes, low concentrations of lidocaine and prilocaine in plasma were observed (0.230 and 0.223 mg/L, respectively) six hours after administration (Essink-Tebbes et al., 1999). Eighteen hours after application, low concentrations of lidocaine and prilocaine were found in one and six neonates, respectively. Thirty hours after administration, lidocaine and prilocaine concentrations in all neonates were below 0.10 mg/L. When EMLA cream (10 g) was applied topically to the face of 10 healthy volunteers for 2 hours, the mean concentrations of lidocaine and prilocaine peaked at 150 ng/mL and 58 ng/mL, respectively, 2 to 2.5 hours after dermal application under occlusion (Juhlin et al., 1989). However, when the same amount was applied to the forearm of the same volunteers under the same conditions, concentrations of lidocaine (18 ng/mL) and prilocaine (<5 ng/mL) peaked 5 hours after application. This clearly shows that the location of dermal application of EMLA plays a large role in the resulting plasma concentrations of lidocaine and prilocaine.

The elimination half-lives of lidocaine, prilocaine, and *o*-toluidine after i.v. injection (25 mg lidocaine, 25 mg prilocaine) in 15 healthy full-term male piglets were 1.9, 1.4, and 5.4 hours, respectively (Gazarian et al., 1995). Clearance after i.v. injection was 26.6 mL/min/kg for lidocaine and 111.4 mL/min/kg for prilocaine.

Although concentrations of lidocaine and prilocaine may be low in the general circulation, they may be higher in the draining veins near the site of topical application of EMLA cream, especially in individuals that have skin conditions with lesions such as psoriasis or dermatitis (Juhlin et al., 1989). These conditions appear to cause more rapid diffusion of anesthetics through the skin causing plasma concentrations of prilocaine and lidocaine in the vein draining the topical site to be 2 to 90 times higher than concentrations in the general circulation. The application of EMLA on lesional skin resulted in more rapid onset and

termination of anesthesia in the applied area. The draining vein concentrations seen in patients with atopic dermatitis (9,560-13,070 ng/mL) that were 90 times higher than general circulation concentrations would be toxic if in the general circulation. The authors also found that the location of the draining vein in relation to the site of topical application influenced the results. Lower concentrations were observed when EMLA was applied to the dorsal rather than the ventral aspect of the forearm.

After topical application of EMLA cream, prilocaine concentrations in plasma are 10-20% lower than that of lidocaine (Juhlin et al., 1989). This may be due to the more rapid metabolism of prilocaine, prilocaine's low plasma binding, or its higher tissue absorption and affinity when compared to lidocaine (Juhlin et al., 1989). When lidocaine and prilocaine were administered together i.m. in 60 female rats, the amount of prilocaine in tissue at the site of injection (tongue) was less than if prilocaine was administered alone (Åkerman et al., 1966). This is probably due to the vasodilatory action of lidocaine, causing more rapid movement of anesthetic away from the area of administration and into the blood.

9.1.2.7 Ropivacaine

9.1.2.7.1 Metabolism of Ropivacaine

For detailed information on individual metabolism studies refer to **Appendix F, Table F-1, Metabolism Studies of Ropivacaine in Humans and Experimental Animals**.

Since ropivacaine is relatively new compared to the other amide local anesthetics in this report, the metabolism studies are fairly recent. The metabolism of ropivacaine is similar to that of bupivacaine and mepivacaine in that dealkylation results in the formation of PPX; however, the common metabolites after ropivacaine and bupivacaine administration do show quantitative differences that will be discussed later. Ropivacaine used clinically is the (*S*)-(□)-enantiomer. The cytochrome P450 enzymes involved in ropivacaine metabolism have been well studied both *in vivo* and *in vitro*. The metabolites of ropivacaine and metabolic pathway are presented in **Table 21** and **Figure 7**, respectively. The *in vitro* and *in vivo* metabolism of ropivacaine is compared in **Table 22**. **Table 20** lists the human and rat isozymes involved in the *in vitro* metabolism of ropivacaine.

Ropivacaine is extensively metabolized in humans since only ≤1.0-1.4% of the ropivacaine dose is excreted in the urine unchanged (Halldin et al., 1996; Arlander et al., 1998;

Scott et al., 1997). The metabolism of ropivacaine was found to be mediated *in vivo* by human P450 enzymes CYP1A2 and CYP3A4 (Arlander et al., 1998; Ekström and Gunnarsson, 1996). Inhibition of CYP1A2 by fluvoxamine strongly enhanced the urinary excretion of (*S*)-PPX and inhibited (*S*)-3'-hydroxyropivacaine excretion while inhibition of CYP3A4 with ketoconazole increased excretion of (*S*)-3'-hydroxyropivacaine and decreased urinary excretion of PPX (Arlander, 1998). *In vitro* metabolism by dealkylation followed by hydroxylation at position 3'- and 4'- of the xylidine moiety by selected rat and human hepatic P450 enzymes resulted in the formation of PPX, 4'-hydroxyropivacaine, and 3'-hydroxyropivacaine (Oda et al., 1995). The human P450 isozymes CYP3A4 and CYP1A2 are also involved in the metabolism of other drugs, such as nifedipine, alfentanil, midazolam, and quinidine, that are commonly administered during anesthesia. This may result in the pharmacokinetic interaction of ropivacaine with other pharmaceuticals metabolized by CYP1A; however, "the lower affinity of ropivacaine for CYP3A and the large amount of the enzyme in the liver most probably make it less likely that drug interactions would occur" (Ekström and Gunnarsson, 1996).

The metabolites detected in the 96-hour urine collection from six healthy volunteers that received ropivacaine hydrochloride monohydrate (50 mg) i.v. were 3'-hydroxyropivacaine (36.9% of the total dose), 2'-hydroxymethylropivacaine (18.5%), PPX (2.8%), 3'-hydroxypipecoloxylidide (2.2%), ropivacaine (1.0%), and 4'-hydroxyropivacaine (0.4%) (Halldin et al., 1996). The relative amounts of metabolites in this study were representative of amounts detected in urine in other human metabolism studies with ropivacaine (Arlander, 1998; Arvidsson et al., 1999). No 4'-hydroxypipecoloxylidide was detected in any *in vitro* studies with human and rat microsomes or *in vivo* studies with humans and rabbits. This is in contrast to the presence of 4'-hydroxypipecoloxylidide (4.9% of the dose) detected in human urine after bupivacaine administration.

Only trace amounts of PPX were detected in urine *in vivo*, compared to the major amounts found to be metabolized *in vitro* with human liver microsomes in the presence of ropivacaine (Ekstrom and Gunnarsson, 1996; Oda et al., 1995). In one patient with liver disease, the recovery of PPX (20% of the dose) in the urine was three times greater than the recovery of 3'-hydroxyropivacaine (7%) (Scott et al., 1997). The mean terminal elimination half-life of PPX in the plasma of 12 healthy volunteers was 8.8 ± 2.8 hours (Arlander, 1998), much longer than the elimination half-life of ropivacaine itself (1.7-2.0 hours) (Emanuelsson et al., 1997; Halldin

et al., 1996). The mean PPX concentration in plasma was 16.6 mg/L 8 hours after ropivacaine administration, but was 77.1 and 4.1 mg/L with concomitant administration of fluvoxamine and ketoconazole, respectively (Arlander et al., 1998).

Table 20. The Ropivacaine Metabolic Activity of Purified Rat and Human Cytochrome P450 Enzymes

Purified Rat Hepatic P450s	Purified Human Hepatic P450s	Ropivacaine Metabolites (nmol · min^{-1} · nmol $P450^{-1}$)		
		PPX	4'-Hydroxyropivacaine	3'-Hydroxyropivacaine
	CYP1A1	0.10	0.09	0.05
	CYP1A2	—	0.04	1.46
CYP1A2		0.09	0.04	0.34
CYP2A2		0.09	—	—
	CYP2A6	—	—	—
CYP2B1		0.04	—	0.03
CYP2B2		—	—	—
	CYP2B6	0.42	—	0.01
CYP2C11		0.40	—	0.02
CYP2D1		0.04	—	0.14
	CYP2D6	—	0.08	0.01
	CYP2E1	—	—	—
CYP2E1		—	—	0.04
CYP3A2		0.04	—	—
CYP3A2*		0.31	—	—
	CYP3A4	3.20	0.09	—

Taken from Oda et al. (1995).
* Mixture of phospholipids: dilauroylphosphatidylcholine, dioleoylphosphatidylcholine, and phosphatidylserine (1:1:1) were used instead of dilauroylphosphatidylcholine.

No 2,6-xylidine was detected in the 96-hour urine collection from six healthy males given an i.v. infusion of ^{14}C-labeled ropivacaine hydrochloride monohydrate (50 mg) using GC and HPLC methods with a limit of quantification of 0.3 □M (Halldin et al., 1996).

The phenolic metabolites of ropivacaine can be sulfonated by liver sulfotransferases. The sulfotransferases that are capable of sulfonating ropivacaine metabolites most efficiently were

M-PST, P-PST-1, and EST (Falany et al., 1999). DHEA-ST and ST1B2 showed no sulfation activity for ropivacaine metabolites. M-PST does circulate in the blood and it is suggested that some sulfation could occur throughout the body (Heroux and Roth, 1988; Wang et al., 1998; both cited by Falany et al., 1999).

No racemization of ropivacaine metabolites occurred in 22 male human volunteers dosed i.v. and intrarectally or in intravenously infused dogs, sheep, or rats (Arvidsson et al., 1994; Halldin et al., 1996).

Some drugs affect the metabolism of ropivacaine *in vitro*. Cimetidine (1 mM), a non-competitive P450 inhibitor, has been shown to inhibit the formation of 4'-hydroxyropivacaine and 2-hydroxymethylropivacaine by 40-50% with human liver microsomes incubated for 30 minutes (Ekström and Gunnarsson, 1996). Addition of high concentrations of sulfaphenazole (100 mM) in the medium inhibited formation of 4'-hydroxyropivacaine, 2-hydroxymethyropivacaine, and PPX by 20-27%. The addition of naphthoflavone or furafylline almost completely inhibited the formation of 3'-hydroxyropivacaine, but did not affect formation of 4'-hydroxyropivacaine, 2-hydroxymethylropivacaine, and PPX.

In vitro studies of ropivacaine metabolism do not accurately reflect *in vivo* metabolism. In all *in vitro* studies, PPX and 4'-hydroxyropivacaine were the major metabolites detected, and 3'-hydroxyropivacaine was a minor metabolite when human and rat hepatic microsomes were incubated with ropivacaine (Oda et al., 1995; Ekström and Gunnarsson, 1996). However, in humans PPX and 4'-hydroxyropivacaine are minor metabolites and 3'-hydroxyropivacaine is the major metabolite (Halldin et al., 1996; Arlander, 1998).

Table 21. Ropivacaine, Its Salts, and Its Metabolites

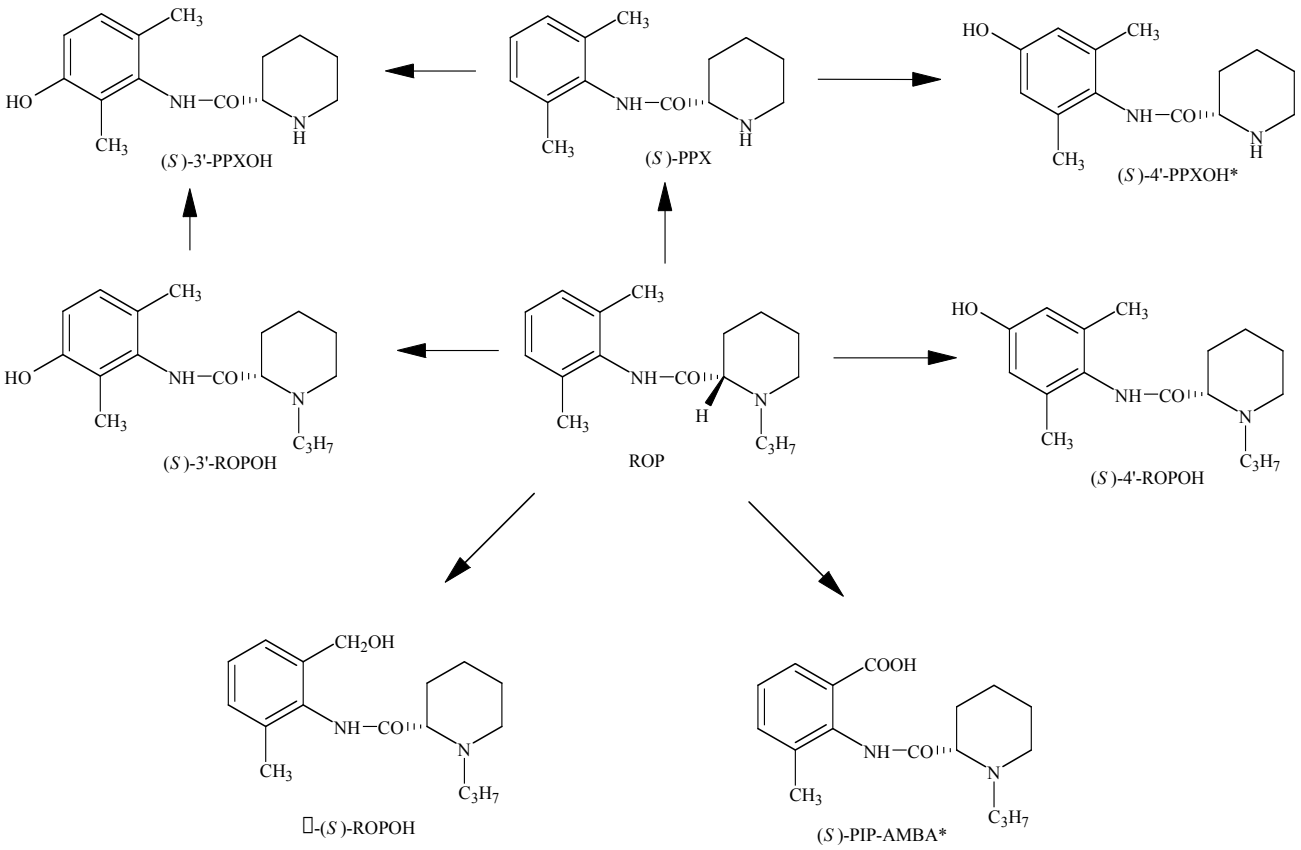
Parent (shaded) or Metabolite Code[a]	Metabolite	Hill Formula	CASRN	Chem. Abstr. References & References Used
(S)-ROP	Ropivacaine; (*S*)-(-)-Ropivacaine; (-)-Ropivacaine; (-)-LEA; (2*S*)-*N*-(2,6-Dimethylphenyl)-1-propyl-2-piperidinecarboxamide; (-)-1-Propyl-2′,6′-pipecoloxylidide	$C_{17}H_{26}N_2O$	84057-95-4	162
(S)-ROP·HCl	Ropivacaine hydrochloride	$C_{17}H_{27}ClN_2O$	98717-15-8	11
(S)-ROP·HCl·H_2O	Ropivacaine hydrochloride monohydrate	$C_{17}H_{29}ClN_2O_2$	132112-35-7	6
(R)-PPX	(*R*)-2′,6′-Pipecoloxylidide; (*R*)-Desbutylbupivacaine; (-)-2′,6′-Pipecoloxylidide **[Very minor.]**	$C_{14}H_{20}N_2O$	27262-43-7	Arvidsson et al. (1995)
(S)-PPX	(*S*)-2′,6′-Pipecoloxylidide; (*S*)-Desbutylbupivacaine; (+)-2′,6′-Pipecoloxylidide; (2*S*)-*N*-(2,6-Dimethylphenyl)-2-piperidinecarboxamide	$C_{14}H_{20}N_2O$	27262-40-4	20 Arlander et al. (1998) Arvidsson et al. (1995)
PPX	2′,6′-Pipecoloxylidide [racemic]; 2′,6′-Pipecolylxylidide; PPX; *N*-Desbutylbupivacaine; Mono-*N*-demethylmepivacaine; *N*-(2,6-Dimethylphenyl)-2-piperidinecarboxamide	$C_{14}H_{20}N_2O$	15883-20-2	45 (Frequently indexed as a ropivacaine metabolite when (S)-PPX [27262-40-4] is meant.)
(S)-3′-ROPOH	(-)-3′-Hydroxyropivacaine; 3′-Hydroxyropivacaine; (*S*)-3′-Hydroxy-1-propyl-2′,6′-pipecoloxylidide; (2*S*)-*N*-(3-Hydroxy-2,6-dimethylphenyl)-1-propyl-2-piperidinecarboxamide	$C_{17}H_{26}N_2O_2$	163589-30-8	8 Halldin et al. (1996)
(S)-4′-ROPOH	(-)-4′-Hydroxyropivacaine; (*S*)-4′-Hydroxy-1-propyl-2′,6′-pipecoloxylidide; (2*S*)-*N*-(4-Hydroxy-2,6-dimethylphenyl)-1-propyl-2-piperidinecarboxamide	$C_{17}H_{26}N_2O_2$	163589-31-9	5 Halldin et al. (1996)

Table 21. Ropivacaine, Its Salts, and Its Metabolites (Continued)

Parent (shaded) or Metabolite Code[a]	Metabolite	Hill Formula	CASRN	Chem. Abstr. References & References Used
(S)-α-ROPOH	(2*S*)-*N*-[2-(Hydroxymethyl)-6-methylphenyl]-1-propyl-2-piperidinecarboxamide; 2-OH-methyl-ropivacaine [*sic*, Ekstrom & Gunnarsson (1996)]	$C_{17}H_{26}N_2O_2$	182703-01-1	2 Halldin et al. (1996)
(S)-PIP-AMBA	"(*S*)-2-Carboxyropivacaine;" 3-Methyl-2-[(1-propylpiperidine-2-carbonyl)amino]benzoic acid; (2*S*)-*N*-[(2-Carboxy)-6-methylphenyl]-1-propyl-2-piperidinecarboxamide **[Falany et al. (1999) conducted *in vitro* sulfation of synthesized known and suspected ropivacaine metabolites. Not derived as a metabolite. Not found in references cited.]**	$C_{17}H_{24}N_2O_4$	Not identified	Falany et al. (1999)
(S)-3′-PPXOH	(*S*)-3′-Hydroxy-2′,6′-pipecoloxylidide; (*S*)-3′-Hydroxy-2′,6′-PPX; (2*S*)-*N*-(3-Hydroxy-2,6-dimethylphenyl)-2-piperidinecarboxamide **[Has not been reported as a bupivacaine metabolite.]**	$C_{14}H_{20}N_2O_2$	182878-70-2	2 Halldin et al. (1996) Arvidsson et al. (1999)
(S)-4′-PPXOH	(*S*)-4′-Hydroxy-2′,6′-pipecoloxylidide; (*S*)-4′-Hydroxy-2′,6′-PPX; (2*S*)-*N*-(4-Hydroxy-2,6-dimethylphenyl)-2-piperidinecarboxamide **[Proposed ropivacaine metabolite, but no evidence for this compound as a human metabolite.]**	$C_{14}H_{20}N_2O_2$	243989-47-1	1 Arvidsson et al. (1999)

[a] (R)- and (S)- prefixes indicate specific optically active enantiomers.
Primes on numbers in codes indicate that ring hydroxylation is on the xylidine or toluidine moiety. Primes are not used on codes for hydroxylated derivatives of xylidine and toluidine. Numbers without primes in codes indicate that substitution is not on the xylidine or toluidine moiety (usually on the pipecolyl moiety).
The lower-case Greek letter alpha in a code indicates that hydroxylation is on a xylidine methyl group.

Figure 7. Metabolic Pathway of Ropivacaine in Humans and Experimental Animals



* conjectural metabolites were not detected in any studies reviewed

Table 22. Metabolites of Ropivacaine Detected *In Vivo* and *In Vitro* and Their Amounts in Human Urine and [Plasma]

Metabolite Code	Range of Mean Amounts of Ropivacaine Metabolites Detected in Urine and [Plasma][a]			
	In Vivo		*In Vitro*	
ROP	X	4.7 M [4.9 M] 1.0%		
(*S*)-PPX	X	23.2 M [1.5 M] 2.8%	X	1847 pmol/mg/min
(*S*)-PIP-AMBA			X	n.q.
(*S*)-3'-ROPOH	X	118 M; 36.9%	X	46 pmol/mg/min
(*S*)-3'-ROPOH	X	0.4%	X	105 pmol/mg/min
-(*S*)-ROPOH	X	trace-18.5%	X	9 pmol/mg/min
(*S*)-3-PPXOH	X	10 0 M; 2.2%		

[a] Urinary excretion = percentage of the administered dose found in the urine. Plasma concentrations are given in micrograms per milliliter.

9.1.2.7.2 Pharmacokinetics of Ropivacaine

For detailed information on individual pharmacokinetics studies refer to **Appendix F, Table F-2, Pharmacokinetics Studies of Ropivacaine in Humans and Experimental Animals**.

The pharmacokinetics of ropivacaine is similar to bupivacaine except that the neuro- and cardiotoxicity of ropivacaine is less, probably associated with the fact that ropivacaine is used as the (S)-enantiomer only and no racemization of ropivacaine or its metabolites occurs after administration. This means that at the same dose or infusion rate, ropivacaine concentrations in the blood are less than those of bupivacaine (Gustorff et al., 1999). Ropivacaine (0.5%) results in less motor block than bupivacaine (0.5%).

The protein-bound fraction of ropivacaine in plasma was observed to be about 95%. In one study of 11 patients undergoing elective orthopedic surgery, the bound fraction of ropivacaine ranged from 85.9% to 98.8% (Scott et al., 1997). Protein binding was observed to increase from the initiation of infusion to the end of the observation period, which was due to increases in the concentration of □-acid glycoprotein during infusion (Erichson et al., 1996; Scott et al., 1997).

The urinary excretion of radioactivity from ^{14}C-labeled ropivacaine hydrochloride was 86% of the dose in 96-hour urine collections from nine healthy human males, which was higher than excretion in rats (~41%) and dogs (63%), but similar to urinary excretion in pregnant rabbits (92%) (Halldin et al., 1996).

The elimination half-life of ropivacaine from venous plasma after epidural infusion (4.2 hours) is much longer than the half-life after i.v. administration, again due to the slow absorption from the epidural space (1.7-2.0 hours) (Emmanuelsson et al., 1995, 1997; Halldin et al, 1996). The plasma concentrations of ropivacaine may or may not plateau during continuous epidural infusion.

After i.v. administration, mean peak plasma concentrations of ropivacaine were 1.23 ± 0.21 mg/L immediately after infusion in 12 healthy human subjects.

It has been suggested that monitoring arterial plasma concentrations of ropivacaine would be better than monitoring venous concentrations since arterial concentrations are higher than venous (Emanuelsson et al., 1997).

The mean total plasma clearance of ropivacaine has been determined to range from 320 to 430 mL/min after epidural and i.v. administration (Emanuelsson et al., 1995, 1997; Arlander 1998; Erichson et al., 1996).

9.1.3 Acute Exposure

Lethal dose values for local anesthetics and their metabolites are presented in **Tables 23** and **24**, respectively.

The discussion in section 9.1.3 of articles and abstracts published from 1963 to 1999 on the acute toxicity of the amide local anesthetics (other than the lethal dose determinations discussed above) is based almost entirely on records retrieved from the databases MEDLINE, TOXLINE, EMBASE, and BIOSIS in December 1999 and January 2000. The amount of experimental detail in the records was highly variable and when present, not always distinguishable for a specific compound. Thus, the discussion is uneven and inconsistent and did not lend itself readily to tabulation. The inclusion of studies is not comprehensive, and only studies in mammals were considered for inclusion. The discussion is intended to give a fair representation of the kinds of studies performed in specific species. The lack of identified studies in pigs noted for etidocaine, mepivacaine, prilocaine, and lidocaine is largely because terms for swine were not included in their search strategies.

9.1.3.1 Bupivacaine

Approximately 150 animal experiments (some *in vitro*) testing the effects of bupivacaine were identified by online searches in January 2000. Studies using rats (~40) and dogs (~30) predominated over studies using other animals. There were 15 studies each for mice, rabbits, and pigs; 13 for sheep, 10 for cats, 8 for monkeys, and 5 for guinea pigs. Studies with exposures of at least one week are described in other subsections. This subsection briefly describes some of the studies involving acute exposures. Adverse effects on the CNS and CVS were the most frequent toxic signs. (The comments are based on abstracts selected from the online database search results.) Muscle degeneration studies comprised a large fraction of the rat studies. Studies in sheep often examined fetal effects during labor.

Table 23. LD_{50} Values (mg/kg) for Local Anesthetics [unless otherwise noted]

Compound and Test System	Route									Toxic Effects
	implant	intramuscular	intraperitoneal	intraspinal	intratracheal	intravenous	oral	parenteral	subcutaneous	
bupivacaine										
guinea pig			36.6							
human						TD_{LO}=4.3				F06, H06
mouse						7.1			35	
rabbit					12.5	1.62		64		
rat						5.6			47	
***D*-(+)-bupivacaine**										
mouse						7.9				
rabbit					10	LD_{LO}=5.5		>120		F12 for i.v.
rat						3.8			38	
***L*-(-)-bupivacaine**										
mouse						9.6			100	
rabbit					14	LD_{LO}=9.7		>120		F12 for i.v.
rat						7.2			52	
etidocaine										
mouse			47.5							
etidocaine hydrochloride										
dog						LD_{LO}=10				
mouse		58.178	64.4			6.7			99	F02, F07 for i.p.
lidocaine										
guinea pig						LD_{LO}=65			120	
human:						TD_{LO}=23				F23, J22

Table 23. LD_{50} Values (mg/kg) for Local Anesthetics [unless otherwise noted] (Continued)

Compound and Test System	Route									Toxic Effects
	implant	intramuscular	intraperitoneal	intraspinal	intratracheal	intravenous	oral	parenteral	subcutaneous	
child							TD_{LO}=21 TD_{LO}=300			F12, H02, J25 F12, H02, U25
man						TD_{LO}=8.643 TD_{LO}=1.700				F10 F24, G08, J25
woman				1 mL/kg		TD_{LO}=16	TD_{LO}=39			F06, F08 for i.s. F08, F13, G10 for oral G10, J22 for i.v.
mouse			102			20	220		238	F12, F21, J26 for oral C17, F12, F19 for i.p. F12, H02, J30 for i.v.
rabbit						LD_{LO}=41				
rat			133			18	317		335	F07, F12, J30 for i.p.
lidocaine hydrochloride										
guinea pig						24.5				
human: child						TD_{LO}=60				F12, H02
infant						TD_{LO}=10	TD_{LO}=1.600 TD_{LO}=1632			F12, F24, J30 for i.v. F12 for oral at 1.600 F07, F12 for oral at 1632
man	TD_{LO}=5.714								TD_{LO}=9 TD_{LO}=7.143	F12 for implant G01 for s.c. at 9 G07 for s.c. at 7.143
dog						LD_{LO}=65.7				
frog								159		
mouse		177	63			15	220		163	F05, J26 for i.v.
rabbit					28	25.6				
rat			122			21			570	
lidocaine hydrochloride monohydrate										
mouse							292			F12

Table 23. LD_{50} Values (mg/kg) for Local Anesthetics [unless otherwise noted] (Continued)

Compound and Test System	Route									Toxic Effects
	implant	intramuscular	intraperitoneal	intraspinal	intratracheal	intravenous	oral	parenteral	subcutaneous	
mepivacaine										
mouse			LD_{LO}=135			35	>5000		270	F07, F11 for i.p.
rabbit						LD_{LO}=53				
rat						30	>5000		500	
mepivacaine hydrochloride										
guinea pig						20			94	
mouse	260		117			32			260	
rabbit	110					22			110	
prilocaine										
mouse			231			59.9			519	F13, J22, R21 for s.c.
prilocaine hydrochloride										
human: man								LD_{LO}=12.343		P01
mouse			30			55			632	
rabbit					65	18				F05, F12 for i.v. and i.t.
rat			148			56.6			790	
***DL*-(±)-prilocaine hydrochloride**										
mouse						37				
***L*-(+)-prilocaine hydrochloride**										
mouse						40			380	
***D*-(-)-prilocaine hydrochloride**										
mouse						39			360	
trimecaine										
cat						LD_{LO}=129				

Table 23. LD_{50} Values (mg/kg) for Local Anesthetics [unless otherwise noted] (Continued)

Compound and Test System	Route									Toxic Effects
	implant	intramuscular	intraperitoneal	intraspinal	intratracheal	intravenous	oral	parenteral	subcutaneous	
mouse			180			187			295	
trimecaine hydrochloride										
mouse			172			50			295	F11, F19, J22 for i.v.
rabbit			95							

Source: RTECS (1999)

Abbreviations: LD_{50} = lethal dose for 50% of test animals; LD_{LO} = lethal dose low—lowest dose (other than LD_{50}) of a substance given by any route other than inhalation reported to have cased death in humans or animals; TD_{LO} = toxic dose low—lowest dose of a substance given by any route other than inhalation reported to have caused toxic effect in humans or carcinogenic, neoplastigenic, or teratogenic effect in humans or animals

Definitions of Toxicity Codes:

F: BEHAVIORAL: 02-anticonvulsant; 05-altered sleep time (including changes in righting reflex); 06-euphoria; 07-somnolence (general depressed activity); 08-hallucinations, distorted perceptions; 10-toxic psychosis; 11-tremor; 12-convulsions or effect on seizure threshold; 13-excitement; 19-ataxia; 21-rigidity (includes catalepsy); 23-muscle contraction or spasticity; 24-coma
G: CARDIAC: 01-cardiomyopathy (including infarction); 07-pulse rate increased without fall in BP; 08-pulse rate; 10-change in rate
H: VASCULAR: 02-BP lowering not characterized in autonomic section (see E codes of RTECS)
J: LUNGS, THORAX, OR RESPIRATIONS: 22-dyspnea; 25-respiratory depression; 26-respiratory stimulation; 30-other changes
P: BLOOD: 01-hemorrhage
R: SKIN AND APPENDAGES: 21-hair
U: NUTRITIONAL AND GROSS METABOLIC: 25-body temperature increase

Table 24. LD_{50} Values (mg/kg) for the Metabolites of Local Anesthetics [unless otherwise noted]

Compound and Test System	Route					Toxic Effects
	inhalation	intraperitoneal	intravenous	oral	skin	
4-hydroxy-2,6-xylidine						
cat				LD_{LO}=412		F01, J24, P24
rat				>500		
MEGX						
mouse				234		F12
pipecolic acid						
mouse		610	2200			
PPX						
mouse		140	45			
***o*-toluidine**						
cat				LD_{LO}=150		F24, J22, P24
frog				LD_{LO}=151		F24, J22, P24
man	TC_{LO}=25 mg/m^3					M10, M14, P24
mouse		150		520		P05, P08, P24 for oral
rabbit				840	3.250 mL/kg	P05, P08, P24 for oral
rat	LC_{50}=862 ppm			670 TD_{LO}=1125 TD_{LO}=10,200		P05, P08, P24 for oral F07, F11, J24 for inhalation P27, U01, Z01 for oral M13, P05, U01 for oral
2,6-xylidine						
mouse				707		
rat				840 TD_{LO}=3150 TD_{LO}=6200 TD_{L0}=13,300 TD_{LO}=20,150		F07, J24, P27 P27 Z01 L30, L70, Y03 A70, L70, P70

Source: RTECS (1999)
Abbreviations: LC_{50} = ; lethal concentration for 50% of test animals; LD_{50} = lethal dose for 50% of test animals; LD_{LO} = lethal dose low—lowest dose (other than LD_{50}) of a substance given by any route other than inhalation reported to have cased death in humans or animals; TD_{LO} = toxic dose low—lowest dose of a substance given by any route other than inhalation reported to have caused toxic effect in humans or carcinogenic, neoplastigenic, or teratogenic effect in humans or animals

Definitions of Toxicity Codes:

A: BRAIN AND COVERINGS: 70-not defined
F: BEHAVIORAL: 01-general anesthetic; 07-somnolence (general depressed activity); 11-tremor; 12-convulsions or effect on seizure threshold; 24-coma
J: LUNGS, THORAX, OR RESPIRATIONS: 22-dyspnea; 24-cyanosis
L: LIVER: 30-other changes in the liver; 70-changes in liver weight
M: KIDNEY, URETER, AND BLADDER: 10-urine volume increased; 13-proteinuria; 14-hematuria
P: BLOOD: 05-normocytic anemia; 08-pigmented or nucleated red blood cells; 24-methemoglobinemia-carboxyhemoglobin; 27-changes in spleen; 70-changes in other cell count (unspecified)
U: NUTRITIONAL AND GROSS WEIGHT: 01-weight loss or decreased weight gain
Y: BIOCHEMICAL: 03-phosphatases
Z: RELATED TO CHRONIC DATA: 01-death in the "U" type

Mice

Bupivacaine doses that induced convulsions in 50% of mice (i.p. CD_{50} = 57.7 mg/kg) were fatal in 90% of the mice with induced seizures (i.p. LD_{50} = 58.7 mg/kg) (de Jong and Bonin, 1980a). Bupivacaine given i.p. was only about 30 to 40% more toxic than when given s.c. (de Jong and Bonin, 1980b). Elderly mice showed less systemic CNS toxicity than immature mice (Liu et al., 1983a). Pretreatment with a benzodiazepine drug markedly decreased lethality and convulsions (de Jong and Bonin, 1981).

Several studies have reported circadian variations in protein binding, tissue binding, tissue concentrations, and erythrocyte membrane permeability of bupivacaine, etidocaine, and mepivacaine in mice (Bruguerolle and Prat, 1989, 1992; Prat and Bruguerolle, 1988, 1990). Others studied muscle degeneration and regeneration after multiple bupivacaine injections (Martin and Ontell, 1988).

Rats

Zavisca et al. (1991) reported the progressive toxicity of bupivacaine during continuous i.v. infusion of anesthetized, tracheostomized, and ventilated rats given bupivacaine at the rate of 2 mg/kg/min. Doses inducing ventricular arrhythmias, seizures, isoelectric EEG, and asystole were 4.22, 7.08, 11.05, and 20.4 mg/kg, respectively. Zavisca et al. (1994) studied strain differences in CVS and CNS toxicity among Sprague-Dawley, spontaneously hypertensive, and Brattleboro rats (with deficient vasopressin turnover).

Subarachnoid infusion of 0.5% bupivacaine for up to 24 hours was associated with a dose-dependent residual paralysis in many of the test rats until sacrifice at 7 days (Li et al., 1985).

Toxic signs in pregnant rats given bupivacaine in s.c. doses of 14 to 24 mg/kg in late pregnancy included chewing, spasm, dyspnea, drowsiness, salivation, convulsion, and death. The reduced offspring survival was attributed to impaired maternal care (Danielsson et al., 1997).

Mets et al. (1992) reported that the cardiorespiratory toxicity of bupivacaine and lidocaine was additive when given by i.v. infusion as a mixture of 0.25% bupivacaine and 1% lidocaine. Propofol and sevoflurane antagonized bupivacaine toxicity, increasing the bupivacaine infusion doses that induced dysrhythmias, seizures, and 50%-heart-rate reduction

(Ohmura et al., 1999). Cardiorespiratory toxicity of i.v. doses of bupivacaine was enhanced by administration of epinephrine and phenylephrine (Kambam et al., 1990).

Muscle degeneration and regeneration after i.m. bupivacaine injections have been studied frequently in rats over the last 30 years (e.g., Benoit and Belt, 1970; Devor and Faulkner, 1999).

Guinea Pigs

Five records that indexed both bupivacaine and guinea pigs were retrieved in the January 2000 search of about 8 databases. Only one record had an abstract, and it lacked any compound-specific data. Two of the records represented only published abstracts (dated 1998 and 1999). Only two records appeared to represent *in vivo* toxicity studies, one of which was on fetal and neonatal toxicity (Finster, 1976) and the other was on the direct cardiotoxicity of bupivacaine entantiomers (Graf et al., 1998 abstr.).

Rabbits

Corneal and retinal toxic effects after topical application or intravitreal injections of bupivacaine were reported by several researchers to be minimal in rabbits (Sun et al., 1999; Liang et al., 1998; Zemel et al., 1995). However, Judge et al. (1997) reported that topical application and anterior-chamber injection of 0.75% bupivacaine hydrochloride produced clinically and statistically significant corneal thickening and opacification in the eyes of rabbits.

Intrathecally administered bupivacaine tested at concentrations up to its solubility limit did not produce the extensive irreversible neurologic and neuropathologic changes observed when rabbits were given lidocaine at concentrations well above those used clinically (Ready et al., 1985). Co-administration of the sedative midazolam reduced and delayed bupivacaine's cardiotoxic effects in arterially cannulated rabbits (Yayci et al., 1999).

Surgically exposed rabbit vagus nerves bathed in 0.75% bupivacaine for one hour showed minor or no histologic abnormalities (Barsa et al., 1982). Malinovsky et al. (1997) found no significant histological changes due to bupivacaine in concentrations up to 0.5% given in three injections 48 hours apart via a catheter implanted in the lumbar epidural space.

Cats

At i.v. infusion rates of 2.5 to 3.8 mg/kg/min, bupivacaine produced short waves in the EEG for a short time before inducing convulsions (Shibata et al., 1994).

Bupivacaine was a potent inducer of neurogenically mediated ventricular arrhythmias (Heavner, 1986), even in normokalemic cats (de Jong et al., 1982a). At topical spray doses inducing arrhythmias, bupivacaine induced apnea in 4 of 6 cats whose airways were anesthetized by the spray (Ford et al., 1984).

Dogs

The mean cumulative convulsive dose of bupivacaine given rapidly and serially i.v. was 5.0 mg/kg in awake dogs (Liu et al., 1983b). The cumulative lethal i.v. dose in anesthetized dogs was 20 mg/kg (Liu et al., 1982). Convulsions induced by rapid i.v. boluses were associated with a 232% increase in cardiac output and an 80% increase in mean arterial pressure (Arthur et al., 1988).

Given i.v. to anesthetized dogs, a dose of 4 mg/kg strongly impaired both electrophysiologic and hemodynamic variables (Bruelle et al., 1996). Supraconvulsant bupivacaine doses in awake dogs caused deaths due to hypotension, respiratory arrest, cardiovascular collapse, and/or ventricular fibrillation (Feldman et al., 1989). Bupivacaine caused dose-dependent vasoconstriction and regional myocardial dysfunction in dog hearts perfused *in situ* (Fujita et al., 1996). Lethal doses in anesthetized dogs caused a progressive decrease in cardiac contractility and mean arterial pressure until death (Finegan et al., 1992). Dogs younger than 13 weeks were more sensitive to the CVS toxicity of i.v. bupivacaine (Riquelme et al., 1987).

Some studies evaluated drug and other treatments to resuscitate animals given lethally convulsive doses (e.g., Feldman et al., 1991). Other studies evaluated drug interactions, e.g., the adverse effect of halothane use with bupivacaine on ventricular contractility and intraventricular conduction (Bertrix et al., 1991) and the antagonism by bupivacaine of the arrhythmic action of epinephrine (Chapin et al., 1980).

Monkeys

Increasing the infusion rate from 0.5 to 2.0 mg/kg/min did not decrease the dose that induced seizures in rhesus monkeys (Malagodi et al., 1977). Plasma concentrations measured during seizure activity were reported by Munson et al. (1975) (few data in the abstract).

Muscle fiber damage and regeneration were evaluated in monkeys up to 48 days after a single i.m. dose of bupivacaine (Carlson et al., 1990; Komorowski et al., 1990 [same group]).

Sheep

Several studies of pregnant ewes and their fetuses focussed on placental transfer and changes in physiological parameters that would affect maternal and fetal well-being. Some studies reported somewhat lower toxicity of (*S*)-bupivacaine (levobupivacaine), which is undergoing preclinical evaluation for use in its own right (Huang et al., 1998).

Toxic effects induced in ewes by bupivacaine given by i.v. infusion at the rate of 0.5 mg/kg/min arose in the order convulsions (5.0 ±0 6 mg/kg), hypotension, apnea, and circulatory collapse (8.5 ± 1.2 mg/kg). The bupivacaine-induced toxicity occurred at similar doses in pregnant and nonpregnant ewes with no difference in serum protein binding (Santos et al., 1995). In another study using the same dosing, cardiovascular collapse occurred at lower doses in pregnant ewes (5.1 ± 0.7 mg/kg) than in nonpregnant ewes (8.9 ± 0.9 mg/kg). The difference between bupivacaine doses inducing CNS toxicity in pregnant and nonpregnant ewes, however, was not statistically significant (Morishima et al., 1985). Given as an i.v. bolus, 45 mg bupivacaine hydrochloride induced convulsions in conscious sheep weighing about 45 kg; deaths occurred in two (of six?) sheep given 80 mg (Rutten et al., 1989).

Given i.v. in successive daily dose increments, bupivacaine at a total mean dose of 3.7 ± 1.1 mg/kg (156 ± 31 mg) induced sudden fatal ventricular tachycardia and fibrillation without hypoxia or acidosis in three sheep and fatal respiratory depression with bradycardia and hypotension in a fourth sheep (Nancarrow et al., 1989). Anesthetized and paralyzed sheep made hypoxic and acidotic were more susceptible to bupivacaine cardiotoxicity (Rosen et al., 1985). In a study of resuscitation measures, cardiovascular collapse was induced in sheep at a mean dose of 3.5 ± 1.2 mg/kg injected within 10 seconds into the right atrium (Kasten and Martin, 1986).

Bupivacaine and levobupivacaine given to sheep by continuous i.v. infusion at subconvulsive doses induced time- and dose-dependent depressions of left systolic contractility and minor effects on blood pressure and heart rate. Doses of at least 75 mg bupivacaine or 100 mg levobupivacaine given i.v. induced convulsions and ventricular arrhythmias, which were less deleterious in ewes dosed with levobupivacaine. Doses of 100 to 200 mg bupivacaine induced fatal ventricular fibrillation, whereas these doses of levobupivacaine induced transient, nonfatal arrhythmias (Huang et al., 1998).

Maternal heart rate was slightly, but significantly, reduced by a one-hour i.v. infusion of levobupivacaine, but central venous and intraamniotic pressure, acid-base status, and uterine blood flow were unaffected (Santos et al., 1999). Bupivacaine given to pregnant ewes at doses giving mean plasma levels of 1.55 to 1.83 μg/mL at the end of infusion did not significantly decrease uterine blood flow or induce fetal deterioration (Santos et al., 1992). Epidural bupivacaine anesthesia in pregnant hemorrhaging ewes had worse effects on maternal hypotension, uterine blood flow, and fetal oxygenation than on nonhemorrhaging pregnant ewes (Vincent et al., 1992).

Pigs

Respiratory arrest was the primary cause of death among spontaneously breathing pigs infused i.v. with lethal doses of bupivacaine or lidocaine (Kambam et al., 1993).

In halothane anesthetized pigs given bupivacaine given i.v. at the rate of approximately 1 mg/kg/min, which induced severe ventricular arrhythmias, an increase in vascular resistance helped maintain blood pressure, thereby masking the severe myocardial depression induced by bupivacaine (Nystrom et al., 1999).

Combinations of epinephrine and bupivacaine were synergistic in producing ventricular arrhythmias in young pigs (Darrow et al., 1994 abstr.). Epinephrine combinations with epidural infusions of bupivacaine did not affect the bupivacaine dose causing CVS collapse in spontaneously breathing intact pigs, but the bupivacaine doses inducing seizures and dysrhythmias were lower (Bernards et al., 1989). Nitrous oxide combined with halothane or isoflurane increased bupivacaine toxicity in young pigs and masked early signs of toxicity (Badgwell et al., 1990).

Co-administration of bupivacaine with lidocaine reduced the risk of cardiac arrhythmias but not other toxic endpoints (Kyttä et al., 1991). Amiodarone blocked the induction of cardiac arrhythmias and over CVS effects in hypercarbic and hypoxic pigs (Haasio et al., 1990).

Young pigs less than two-weeks-old succumbed to bupivacaine-induced asystole at lower infusion doses when the pigs were hypercapnic and hypoxic and received halothane than when they were simply hypercapnic (Heavner et al., 1995). Toxic endpoints observed in hypoxic pigs during bupivacaine i.v. infusion were seizures, arrhythmias, isoelectric encephalogram, and asystole (Heavner et al., 1992).

9.1.3.2 Etidocaine

Mice

The incidence of convulsions induced by etidocaine (i.p. EC_{50} = 54.9 mg/kg) was reduced to about 3 to 7% by i.m. pretreatment with benzodiazepine drugs (de Jong and Bonin, 1981). Liu et al. (1983a) found that elderly mice were less susceptible than immature mice to the acute systemic toxicity of highly lipid-soluble etidocaine and bupivacaine.

Circadian variations in protein and tissue binding, tissue levels, erythrocyte permeability, pharmacokinetics, and acute toxicity in mice were studied by Bruguerolle and Prat (1989, 1990, 1992) and Prat and Bruguerolle (1990).

Rats

Etidocaine injected perineurally was more potent in motor nerve conduction blockage and induced more nerve injury in rats than lidocaine (Kalichman et al., 1993). The histopathological changes in rat sciatic nerve induced by extraneural injections of etidocaine, lidocaine, and other local anesthetics were concentration-dependent (Kalichman et al., 1989).

Guinea Pigs

No compound-specific testing results were available in the database records for five publications whose indexing included the term guinea pigs.

Rabbits

Adams et al. (1974) reported on spinal cord morphological effects of etidocaine administered intrathecally to rabbits.

Cats

Adverse CNS and CVS effects of etidocaine in cats have been studied by Shibata et al. (1994) and de Jong et al. (1982b).

Dogs

Etidocaine induced convulsions in awake dogs after rapid i.v. administration at a mean cumulative dose of 8.0 mg/kg (Liu et al., 1983b), and the cumulative lethal i.v. dose of etidocaine in anesthetized ventilated dogs was 40 mg/kg (Liu et al., 1982). Etidocaine clearance of a 30-second i.v. bolus in convulsing dogs was reduced 60% compared to that of dogs receiving a nonconvulsing dose (Arthur et al., 1988).

Etidocaine as well as bupivacaine and lidocaine protected anesthetized dogs from arrhythmic effects of epinephrine (Chapin et al., 1980).

Monkeys

Increasing the i.v. infusion rate from 0.5 to 2.0 mg/kg/min decreased the etidocaine dose inducing seizures in monkeys (Malagodi et al., 1977). Intravenous infusion doses and plasma levels of etidocaine and bupivacaine that induced seizures in monkeys were similar and about four times lower than the corresponding doses and plasma levels of lidocaine (Munson et al., 1975). Intravenous etidocaine doses induced CNS toxicity in monkeys that was simply additive when used in mixtures with lidocaine and tetracaine (Munson et al., 1977).

Sheep

Intravenous infusions of etidocaine at the rate of 0.5 mg/kg/min into fetal, newborn, and adult sheep induced CNS and CVS symptoms in the order convulsions, hypotension, respiratory arrest, and circulatory collapse, with the fetus being the most sensitive (Morishima et al., 1983).

Adams et al. (1982) reported on the spinal cord pathology induced in sheep by etidocaine hydrochloride.

Pigs

No information was identified.

9.1.3.3 Lidocaine

No effort was made for this report to collect and summarize the lidocaine toxicity literature. The comprehensiveness of literature searches was complicated by the sheer numbers of lidocaine publications in the biomedical databases searched. Combining the answer set with terms that should not appear in the records using the Boolean operator NOT seemed to be a reasonable strategy to reduce the number of retrievals. However, desirable records were lost. A 40% increase in originally identified acute toxicity publications including lidocaine occurred after searching for acute toxicity publications on the other amide local anesthetics. Therefore, many of the publications discussed in section 9.1.3 also included lidocaine in their studies. The minimum number of unique publications on *in vivo* animal acute toxicity studies that included lidocaine (including dermal sensitization and generally excluding those cited in RTECS) are given below for each species.

Mice: 28

Rats: 50 (including three on fetal toxicity)

Guinea Pigs: 13 (including one on fetal toxicity)

Rabbits: 18 (including one on fetal toxicity)

Cats: 18

Dogs: 38 (including one on fetal toxicity)

Monkeys: 17 (including two on fetal toxicity)

Sheep: 19 (including 12 fetal toxicity studies)

Pigs: Unknown; "pig OR pigs OR swine" were not included in the search terms.

9.1.3.4 Mepivacaine

Mice

Few mepivacaine studies have been done with mice *in vivo*. Mepivacaine was included in the chronotoxicity studies reported by Prat and Bruguerolle (1988, 1990) and Bruguerolle and Prat (1989, 1992).

Giving mice mepivacaine hydrochloride at doses 40 mg/kg and 60 mg/kg (route not provided in the abstract) significantly increased hexabarbital-induced sleeping time when pretreatment was short-term but not when it was long-term (Richuse and Smudski, 1975).

Rats

Older studies have examined convulsive properties (Dobbs and Ross, 1968), tissue damage (Bjoerlin, 1964), and edema (Holroyd and Watts, 1963) induced by mepivacaine and other local anesthetics.

Mepivacaine was among the local anesthetics inducing endoneural edema in sciatic nerves of rats injected into surrounding soft tissue and fascia (Kalichman et al., 1988).

Single and repeated i.m. injections of 2% mepivacaine induced degeneration and regeneration in skeletal muscle structure. Foci of increased interstitial connective tissue persisted after repeated injection (Basson and Carlson, 1980).

Guinea Pigs

Only one *in vivo* toxicity study testing mepivacaine in guinea pigs was identified. Finster (1976) studied mepivacaine toxicity in fetal and newborn guinea pigs (no experimental information was given in the online record).

Rabbits

No online abstract was available for a Japanese-language publication (Fukushima et al., 1986) reporting a study testing mepivacaine for skin irritation in rabbits.

Cats

Cats, as well as rats, guinea pigs, and dogs, were used in early studies of mepivacaine pharmacology (Helmy et al., 1967) and the enhancement of mepivacaine CNS toxicity by metabolic respiratory acidosis (Englesson, 1974; Englesson and Matousek, 1975).

Shibata et al. (1994) showed that slow infusion rates (e.g., 1 mg/kg/min for mepivacaine) of both ester and amide local anesthetics elicited a tetraphasic sequence of changes in brain electrical activities. High mepivacaine infusion rates induced sudden epileptic brain activities in contrast to etidocaine and bupivacaine, which produced slow waves for a short time before the onset of seizure activities.

Dogs

At least 14 mepivacaine toxicity studies have used dogs. In several studies of cardiotoxicity in dogs, mepivacaine usually showed intermediate toxicity among the local anesthetics.

The cumulative lethal i.v. dose of mepivacaine in anesthetized ventilated dogs was comparable to that of lidocaine (~80 mg/kg). A dose of 10 mg/kg induced moderate depression (Liu et al., 1982).

At doses causing convulsions given as a 30-second i.v. bolus, total body clearance of mepivacaine in dogs decreased by 68%, heart rate increased by 129%, and cardiac output increased by 78% (Arthur et al., 1988).

In a study comparing electrophysiologic and hemodynamic effects of amide local anesthetics in anesthetized dogs, mepivacaine given at an i.v. dose of 12 mg/kg was moderately cardiotoxic, whereas lidocaine, bupivacaine, and etidocaine had stronger effects. Mepivacaine induced only slight changes in electrophysiologic variables and transient hemodynamic depression (Bruelle et al., 1996).

Dogs have been used in mepivacaine studies of effects on enzymes (e.g., monoamine oxidase inhibition [Heavner et al., 1986]), differential cell counts and hormones in blood during epidural anesthesia (Nava et al., 1984), systemic effects of dental injections (Smith and Pashley, 1983), and acid-base influences on toxicity (e.g., Englesson, 1966).

Monkeys

No online abstract was available for the studies of seizures induced by mepivacaine, lidocaine, and prilocaine (Munson et al., 1970).

Severe skeletal fiber degeneration and regeneration in monkeys injected i.m. with 2% mepivacaine followed a course similar to that reported in rats (Komorowski et al., 1990; Carlson et al., 1990). Periodontal ligament injections of mepivacaine at 30 mg/mL over 5 to 20 seconds induced immediate cell damage in adjacent tissues, which recovered in one week (Anneroth et al., 1985).

Sheep

Pregnant sheep were no more susceptible than nonpregnant ewes to the toxicity of mepivacaine administered by i.v. infusion at 2 mg/kg/min. Toxic symptoms arose in the order convulsions, hypotension, respiratory arrest, and circulatory collapse (Santos et al., 1989). Like bupivacaine, lidocaine, and procaine, intravascular mepivacaine decreased blood flow in pregnant and nonpregnant ewes. The anesthetics stimulate vasoconstriction and myometrial contractility, thereby reducing blood flow to the placental and nonplacental vascular beds of the pregnant ewes (Greiss et al., 1976).

Pigs

No information was identified.

9.1.3.5 Prilocaine

Mice

Prilocaine, lidocaine, and some ester local anesthetics given to mice i.p. induced locomotor inhibition with potencies similar to their potencies in interacting with sodium channels (Reith et al., 1985).

Rats

Prilocaine convulsive properties in rats were reported by Dobbs and Ross (1968). Experiments allowing comparison of the neurotoxicity of intrathecal prilocaine and lidocaine were recently reported in a published abstract (Kishimoto et al., 1998 abstr.). Drugs potentiating

the CNS toxicity of prilocaine in rats included mepivacaine pretreatment, morphine, promethazine, and pentazocine (Dietz and Dobbs, 1974). The anticonvulsive properties of i.v. prilocaine and other local anesthetics in organophosphate intoxication were studied by Rump and Kaliszan (1969).

In rats in which EMLA had been applied to the middle ear, auditory brain-stem responses (ABR) and cochlear morphology were damaged. Inner hair cells were less vulnerable than outer hair cells (Anniko et al., 1989; Schmidt et al., 1990).

The mean prilocaine dose inducing asystole in lightly anesthetized rats was 166 mg/kg. The mean dose producing seizure activity in rats was 53 mg/kg (Rosenberg et al., 1993).

Benoit (1978) reported on skeletal muscle damage and regeneration in rats given single i.m. injections of prilocaine and lidocaine. Epinephrine in concentrations $\geq$ 5 µg/mL caused similar but less extensive damage. De Carvalho et al. (1976) reported on prilocaine-induced adverse effects observed in rat s.c. connective tissues after s.c. injection.

Guinea Pigs

Early prilocaine toxicity studies and clinical trials were reported by Paradis and Camougis (1968). (The database record indexes guinea pigs without details.)

Prilocaine was tested for dermal sensitivity in guinea pigs by Aldrete and Klug (1970). (No experimental information was given in the database record.)

EMLA (the eutectic mixture of lidocaine and prilocaine) was ototoxic after instillation into the middle ear of guinea pigs, severely damaging the organ of Corti in the first 4 mm from the round window (Anniko and Schmidt, 1988). Application of EMLA to the tympanic membrane caused minor structural changes in the rat but scarcely any change in the guinea pig (Schmidt et al., 1988).

Karlsson and Persson (1984) studied the inhibition by prilocaine and lidocaine of noncholinergic neural contractions in guinea pig airways (no abstract in the database record).

Prilocaine was among the local anesthetics whose toxicity to the fetus and newborn was examined by Finster (1976).

Rabbits

Rabbits have been used to study vasoconstrictive properties (e.g., Goldman et al., 1966) and adrenergic blocking properties (Sharaf et al., 1977) of prilocaine.

Cats

Cats given prilocaine at high rates of infusion (at least 30 mg/kg/min) did not exhibit seizure activities in the EEG. Idioventriculr rhythm accompanied slow waves and isoelectrical EEG and was followed by ventricular fibrillation (Shibata et al., 1994). Several older database records indexed using the word cats provided no prilocaine-specific information.

Dogs

Anesthetized dogs administered prilocaine i.v. at 10 mg/kg showed moderate signs of CVS depression (Liu et al., 1982). Studying nerve-intact dog hearts *in situ*, Satoh (1981) reported that the initial decreased heart rate induced by prilocaine was inhibited by propranolol given in the sinus node artery and was suppressed by reserpine pretreatment. Earlier dog studies include one on induction of methemoglobinemia (Sadove et al., 1965) and seizure induction (Englesson et al., 1965).

Monkeys

Munson et al. (1970) reported on the prilocaine induction of seizures in rhesus monkeys.

Enamel hypoplasia and/or hypomineralization were observed in 15 of 16 permanent teeth of two monkeys 22 months after periodontal ligament anesthesia in the vicinity of the 16 corresponding primary teeth (Brannstrom et al., 1984).

Sheep

No studies were identified.

Pigs

No studies were identified.

9.1.3.6 Ropivacaine

Mice

No studies were identified.

Rats

Pregnant rats receiving ropivacaine by s.c. injection at doses up to 26 mg/kg had less severe reactions than those induced by bupivacaine at comparable doses. No rats died from convulsions. Litter size and offspring weight at birth were not affected (Danielsson et al., 1997).

Clinically relevant ropivacaine doses (e.g., 5 mg/mL) induced only minor blood flow changes in the exposed spinal cords of anesthetized rats whereas 20 mg/mL (200 µg given by intrathecal injection) induced a transient reduction in spinal blood flow (Kristensen et al., 1996).

Guinea Pigs

A recent published abstract (Graf et al., 1998 abstr.) reported on the direct cardiotoxicity of the optical isomers of ropivacaine and bupivacaine [no abstract was given in the BIOSIS record].

Rabbits

No studies were identified.

Cats

No studies were identified.

Dogs

Rapid i.v. injections of ropivacaine at 4.9 mg/kg induced convulsions and increases in heart rate and mean arterial blood pressure. All dogs given twice the convulsive dose 48 hours later could be resuscitated (Feldman et al., 1991).

The arterial plasma concentration of ropivacaine after a convulsive dose (4.88 ± 0.47 mg/kg delivered by i.v. injection at the rate of 2 mg/kg/min) was 11.4 ± 0.9 µg/mL. Hypotension, respiratory arrest, and cardiovascular collapse preceded death in one of the dogs

given twice the convulsive dose 24 hours later. One of the survivors had transient premature ventricular contractions (Feldman et al., 1989).

Epidural administration to dogs of either 1% ropivacaine or 0.75% bupivacaine with and without epinephrine twice 48 hours apart decreased mean arterial blood pressure and cardiac output in all groups. Generally, no differences were observed in induced hemodynamic changes (Hurley et al., 1991).

Ganen et al. (1998 abstr.) reported on the spinal cord nerve damage induced by 1% ropivacaine or 2% lidocaine.

Monkeys

No studies were identified.

Sheep

The mean convulsive dose of ropivacaine hydrochloride given as an i.v. bolus was 60 mg. The arterial blood concentration was 20 mg/L. Like bupivacaine, convulsive doses of ropivacaine increased heart rate, mean arterial pressure, pulmonary artery pressure, cardiac output, systemic vascular resistance, left ventricular and diastolic pressure, and myocardial contractility. Doses of 90 and 120 mg induced death due to ventricular fibrillation in two sheep (Rutten et al., 1989).

Intravenous infusions of ropivacaine at 0.5 mg/kg/min induced convulsions at 7.5 mg/kg and circulatory collapse at 12.9 mg/kg. No toxicity differences were observed between pregnant and nonpregnant ewes (Santos et al., 1991, 1995).

The mean fatal dose of ropivacaine was 325 ± 108 mg (7.3 ± 1.0 mg/kg) when given i.v. in successive daily dose increments. Three of the five ropivacaine-treated sheep died after respiratory depression, bradycardia, and hypotension with ventricular arrhythmias. Another sheep died of ventricular fibrillation (Nancarrow et al., 1989).

Pregnant ewes given ropivacaine infusions showed no effects on maternal blood pressure, central venous and intra-amniotic pressures, acid-base status, and uterine blood flow. Fetal wellbeing was not affected (Santos et al., 1992, 1999).

Pigs

Subcutaneous injections of 10 mL of 0.25% ropivacaine did not decrease capillary blood flow or reduce bleeding from surgical incisions (Guinard et al., 1991).

A recent published abstract (Morrison et al., 1998 abstr.) described the cardiotoxicity of ropivacaine as well as that of racemic bupivacaine and levobupivacaine in anesthetized pigs.

9.1.4 Short-Term and Subchronic Exposure

9.1.4.1 Bupivacaine

The details of the following studies are presented in **Table 25**.

In male rats, intrathecal implantation of 0.75% bupivacaine for up to eight days caused sensory anesthesia, which was associated with variable degrees of motor weakness in the tail (Drasner et al., 1994).

When injected into the right plantaris muscle of rats daily for ten weeks, muscle degeneration and regeneration occurred, as evidence by the increase and decrease of serum creatine kinase (CK) activities. The mean weights of plantaris muscle and the number of total branched fibers were increased compared to controls (untreated contralateral plantaris). Aggregations of same-type fibers, complex branched fibers, and some anastomosing syncytial reticulum were observed. Maximum absolute twitch and tetanic tensions were also higher compared with controls (Tamaki and Akatsuka, 1994; Tamaki et al., 1997).

When anesthetic-impregnated silastic cuffs containing 5-60% by weight bupivacaine were implanted into the soleus and/or lumbricalis muscles of rats and rabbits for three to 11 days, acetylcholine sensitivity was found in all muscle fibers. Cuffs containing 20% bupivacaine resulted in anesthesia for up to ten days in rats, while cuffs containing >40% bupivacaine resulted in anesthesia for longer than one day in rabbits (Lorkovic, 1975).

In pigs, epidural administration and infusion of bupivacaine for seven days caused slight inflammatory changes in ligamentum flavum and dura mater. One pig had a bacterial infection along the epidural catheter. Inflammatory changes in the epidural space may have been due to catheter irritation (Kyttä et al., 1986).

In dogs, continuous intrathecal infusion for three to 16 weeks caused a markedly decreased response to toe-pinch of the hind limbs. No weakness in the forelimbs was observed. When bupivacaine infusion was stopped, all 16-week animals except one returned to fully

normal gait. A focal infiltration of the leptomeninges by mononuclear cells was observed in two animals. No damage to the dorsal or ventral roots and no pathology within the spinal cord substance were seen. Additionally, no animal exhibited any loss of appetite during the study or difficulty with urination or defecation (Kroin et al., 1987).

9.1.4.2 Lidocaine

[Four potential studies are available. The papers have not been retrieved.]

9.1.4.3 Other Amide Local Anesthetics

No short-term or subchronic studies were identified for the other amide local anesthetics by an extensive literature search in January 2000.

Table 25. Short-term and Subchronic Exposure to Bupivacaine

Species, Strain, and Age	Number and Sex of Animals	Chemical Form and Purity	Route, Dose, and Duration	Observation Period	Results/Comments	Reference
Rats						
Rats, Sprague-Dawley, ages n.p.	8 M	bupivacaine, purity n.p.	intrathecal catheter implantation; infusion of 0.75% compound into the subarachnoid space for 1 hr on day 0, 2 hr on day 4, and 4 hr on day 8	14 days	During all infusions, all rats developed sensory anesthesia, which was associated with variable degrees of motor weakness in the tail (decreased spontaneous movement, failure to lift the tail while ambulating, and loss of normal tone of the tail). During the third infusion, two rats experienced seizures and died. Additionally, a portion of the tail of one rat demonstrated no response to the heat stimulus 6 days after the infusion.	Drasner et al. (1994)
Rats, Wistar, 12-wk-old	5 M	bupivacaine hydrochloride, purity n.p.	i.m. injection; 0.15 mL of 0.5% w/v compound in saline into the right plantaris muscle 1x/wk for 10 wk	11 wk	Muscle degeneration and regeneration occurred. Serum creatine kinase (CK) activities significantly increased 1 hr after the first week and then decreased after the second week. This increasing pattern of CK activities occurred until the tenth week. The number of total branched fibers was increased compared to controls. Aggregations of fibers of the same type were found in various areas. Complex branched fibers and some anastomosing syncytial reticulum were also observed.	Tamaki and Akatsuka (1994)

Table 25. Short-term and Subchronic Exposure to Bupivacaine (Continued)

Species, Strain, and Age	Number and Sex of Animals	Chemical Form and Purity	Route, Dose, and Duration	Observation Period	Results/Comments	Reference
Rats, Wistar, 14-wk-old	M (number n.p.)	bupivacaine hydrochloride, purity n.p.	i.m. injection; 0.15 mL of 0.5% w/v compound in saline into the right plantaris muscle 1x/wk for 10 wk	12 wk Measurement of contractile properties was performed 2 wk after last injection; after measurement, muscles were excised and weighed and prepared for analyses.	The mean weight of plantaris muscle was significantly higher (13%) compared with control (untreated contralateral plantaris). An 8-fold increase in the number of branched fibers in the plantaris muscles (~70% complex branched fibers) was observed. Maximum absolute twitch and tetanic tensions were 19 and 30% higher, respectively, compared with control. The time to peak extension of twitch and tetanus and twitch one-half relaxation time were significantly longer, representing a shift to slow muscle characteristics. Aggregates of same-type fibers (slow fibers) were also observed.	Tamaki et al. (1997)
Rats, Simonsen, "adult"	F, number n.p.	bupivacaine, purity n.p.	implantation of anesthetic-impregnated silastic cuffs containing 5-60% by weight of compound into soleus and lumbricalis muscles for 3-11 days	11 days	When cuffs contained 20% bupivacaine, the sciatic nerves survived and anesthesia was maintained for up to 10 days. Acetyl-choline (ACh) sensitivity was found in the extrajunctional area of all muscle fibers; those displaying miniature end-plate potentials exhibited the spreadout type.	Lorkovi_ (1975)
Rabbits, new Zealand white, ages n.p.	M, number n.p.	bupivacaine, purity n.p.	implantation of anesthetic-impregnated silastic cuffs containing 5-60% by weight of compound into lumbricalis muscles for 3-11 days	11 days	When cuffs contained >40% bupivacaine, the tibial nerves survived and full local anesthesia was maintained for longer than 1 day. ACh sensitivity was found in the extrajunctional area of all muscle fibers; those displaying end-plate potentials exhibited the spreadout type.	Lorkovi_ (1975)

Table 25. Short-term and Subchronic Exposure to Bupivacaine (Continued)

Species, Strain, and Age	Number and Sex of Animals	Chemical Form and Purity	Route, Dose, and Duration	Observation Period	Results/Comments	Reference
Pigs, strain and age n.p.	8 (epidural) 3 (infusion); sex n.p.	bupivacaine, purity n.p.	epidural; 4 mL of 0.5% compound 2x/day for 7 days infusion; 16 mL of 0.25% compound for 12 hr	3 wk	Slight inflammatory changes in ligamentum flavum and dura mater of the spinal cord were observed. There were minimal inflammatory changes in one of two pigs recovering for 3 wk. Also, one pig had a bacterial infection (*Staphylococcus aureus*) all along the epidural catheter; the overall level of bupivacaine plasma concentration in the animal decreased during the week after injection. Inflammatory changes in epidural space may have been due to catheter irritation.	Kyttä et al. (1986)
Dogs, Mongrel, ages n.p.	5 M and F	bupivacaine hydrochloride, purity n.p.	intrathecal catheter infusion with implantable pump system; 5.7-11.1 mg of 0.15-0.37% compound continuously for 3-16 wk	16 wk	No animal showed any weakness in the forelimbs during the study, but all dogs did show a markedly decreased response to toe-pinch of the hind limbs during infusion. When bupivacaine infusion stopped, all animals, except one (foot droop) returned to fully normal gait. A focal infiltration of the leptomeninges by mononuclear cells was observed in two animals (at a dose of 9.3 and 10.4 mg). There was no evidence of axonal degeneration, demyelination, edema, or proliferation of mononuclear (arachnoid or lymphocyte) cells. No animal showed any damage to the dorsal or ventral roots. There was also no pathology within the spinal cord substance.	Kroin et al. (1987)

Abbreviations: ACh = acetylcholine; CK = creatine kinase; F = females; hr = hour(s); i.m. = intramuscular; M = males; n.p. = not provided; wk = week(s)

9.1.5 Chronic Exposure

9.1.5.1 Bupivacaine

The details of the following studies are presented in **Table 26**.

In rats, injection of bupivacaine into the right anterior tibial muscle daily for six months caused muscle fibers to be smaller than controls. Numerous internal nuclei, extensive fiber splitting, whorling of the intermyofibrillar network, and an enlarged zone of terminal innervation were also observed (Sadeh et al., 1985).

In newborn mdx mice and C57BL/10ScSn mice serving as controls, bupivacaine was injected into the right soleus muscle intermittently for up to nine or 12 months. At nine months, the muscle of the mdx mice had much variability in muscle fiber size, but there was no significant pathological difference between the bupivacaine-injected right soleus muscles and the saline-injected left soleus muscles. There was an increase in the percent small fibers compared with control mice. At nine and 12 months, the pattern of distribution of the fiber diameter in the right soleus muscles was more evenly distributed than the left muscles, while the pattern of distribution in the right muscle did not differ from the left in control mice. In mdx mice, endomysial collagen content was 4.6 and 7.2 times that of control mice at nine and 12 months of age, respectively, after injection (Itagaki et al., 1995).

9.1.5.2 Lidocaine

[Three potential studies are available. The papers have not been retrieved.]

9.1.5.3 Other Amide Local Anesthetics

No studies were available.

Table 26. Chronic Exposure to Bupivacaine

Species, Strain, and Age	Number and Sex of Animals	Chemical Form and Purity	Route, Dose, and Duration	Observation Period	Results/Comments	Reference
Rats, Sprague-Dawley, 3-mo-old	9 M	bupivacaine, purity n.p.	i.m. injection; 0.6 mL of 0.75% compound into the right anterior tibial muscle 1x/wk for 6 mo	8 mo After 6 mo, rats were allowed to recovery for 2 mo before being killed; muscles were excised and divided, and some samples frozen for analyses.	Muscle fibers, showing a rounded shape, were smaller than controls and had marked variability in size. Numerous internal nuclei, extensive fiber splitting, and whorling of the intermyofibrillar network were also observed. Cholinesterase and nerve staining showed an enlarged zone of terminal innervation.	Sadeh et al. (1985)
Mice, mdx, "newborn"	12, sex n.p.	bupivacaine, purity n.p.	i.m. injection; 0.1 mL of 0.5% compound into mid-portion of right soleus muscle at 7 wk after birth and then repeated every 4 wk for 9 or 12 mo	at 9 and 12 mo of age, half of mice killed	At 9 months, the soleus muscle had much variability in muscle fiber size (increased endomysial collagen content, slight focal necrosis, and centrally nucleated fibers), but there was no significant pathological difference between right soleus muscles and left (saline-injected) muscles. At 9 and 12 months, the pattern of distribution of the fiber diameter for the right soleus muscles was more evenly distributed that that for the left muscles. The ratio of connective tissue area to cross-sectional muscle area and endomysial collagen content increased with age. However, there was no significant difference between the right and left soleus muscles in content.	Itagaki et al. (1995)

Table 26. Chronic Exposure to Bupivacaine (Continued)

Species, Strain, and Age	Number and Sex of Animals	Chemical Form and Purity	Route, Dose, and Duration	Observation Period	Results/Comments	Reference
Mice, C57BL/10ScSn "newborn"	12, sex n.p.	bupivacaine, purity n.p.	i.m. injection; 0.1 mL of 0.5% compound into mid-portion of right soleus muscle at 7 wk after birth and then repeated every 4 wk for 9 or 12 mo	at 9 and 12 mo of age, half of mice killed	There was no significant variability in muscle fiber size. About 70-80% of the right soleus muscles showed centronucleation. At 9 and 12 months of age, the pattern of distribution of the fiber diameter in the right soleus muscles did not differ from that of the saline-injected left muscle. The endomysial collagen content did not increase with age, and there was no significant difference between the right and left soleus muscles in content.	Itagaki et al. (1995)

Abbreviations: i.m. = intramuscular; M = males; mo = month(s); n.p. = not provided; wk = week(s)

9.1.6 Synergistic/Antagonistic Effects

Lechat and Giroud (1971) have reviewed the synergistic effects of various substances with local anesthetics. Discussed were the results of a mixture of two or more local anesthetics; the effects of the addition of another substance (vasoconstrictors, potassium salts, sugar, hyaluronidase, carbon dioxide, polymers, surfactants, histamine, serotonin, cholinergic substances, antipyretic analgesics, thiamine, urea, sulfonamides, isoniazide, and deuterium oxide) to the solutions of local anesthetics; the effects of the prior administration of certain drugs (narcotic analgesics, neuroleptics, antidepressants, and histamine) on the action of local anesthetics; the reappearance of local anesthesia; and, lastly, the effects of extrinsic factors (environment and pathological state). In many cases, the local anesthetics were generalized into a group. However, some specifics were reported and can, therefore, by given here.

No synergism or antagonism has been observed in mixtures of either amide-amide or amide-ester local anesthetics (Feldman, 1994). A combination of lidocaine with tetracaine applied as a surface anesthesia in humans resulted in no increase in the duration of anesthesia (Lechat and Giroud, 1971).

Vasoconstrictors (commonly epinephrine), added to solutions of local anesthetics to limit the diffusion of the latter and thus increase their action, have variable results, depending on the local anesthetic used and type of anesthesia. In surface anesthesia, epinephrine and norepinephrine increased the action of local anesthetics at the superficial level, while they had no effect in lingual anesthesia. At the endobronchial level, results were ambiguous. In infiltration, conduction, spinal, and epidural anesthesia, vasoconstrictors increased the duration of anesthesia (Lechat and Giroud, 1971). **Table 27** presents data for the local anesthetics discussed in this report.

With the commonly used vasoconstrictors epinephrine and norepinephrine, greater activity with the former versus the latter was observed in conduction and infiltration anesthesia (Lechat and Giroud, 1971). **Table 28** presents data for the local anesthetics discussed in this report.

Table 27. Effects of Vasoconstrictors on Local Anesthetics

Species	Local Anesthetics	Vasoconstrictor	Anesthetized Mucosa[a]/Nerval Fiber[b]/Type of Anesthesia[c]	Modification of the Anesthetic Effect
Surface Anesthesia[a]				
human	lidocaine	epinephrine	bronchial	anesthesia delayed
human	mepivacaine	epinephrine	bronchial	anesthesia delayed
rat mouse	lidocaine	epinephrine	bronchial	toxicity increased
rabbit	mepivacaine	epinephrine	cornea	anesthesia increased
Infiltration Anesthesia				
human	lidocaine	epinephrine felypressin		duration increased
human	prilocaine	epinephrine		duration increased
guinea pig	lidocaine	epinephrine felypressin		duration increased
Conduction Anesthesia[b]				
human	mepivacaine	epinephrine	brachial nerve femoral nerve	unaltered
human	lidocaine	norepinephrine epinephrine	dental root	duration and intensity increased
human	lidocaine prilocaine mepivacaine	epinephrine	cubital nerve	duration increased
human	prilocaine	epinephrine	mandibular nerve	duration increased
rat	lidocaine	epinephrine norepinephrine	sciatic nerve	anesthesia increased
rat	prilocaine lidocaine	epinephrine	sciatic nerve	duration increased
rat	prilocaine	epinephrine felypressin	sciatic nerve	duration increased
Spinal and Epidural Anesthesia[c]				
human	lidocaine	epinephrine	epidural	duration increased
human	lidocaine	epinephrine	peridural	induction time unchanged
human	prilocaine	norepinephrine	spinal	induction time and duration unchanged
human	mepivacaine	epinephrine	epidural	duration very slightly increased
cow	lidocaine	epinephrine	epidural	duration increased

Source: Lechat and Giroud (1971)

Table 28. Comparison of the Effects of Epinephrine and Norepinephrine on Various Types of Local Anesthesia

Species	Type of Anesthesia	Local Anesthetic	Activity
Rat	Conduction	lidocaine	epinephrine > norepinephrine
Man	Dental root	lidocaine	norepinephrine > epinephrine
Rabbit Rat Guinea pig	Surface and spinal Conduction Infiltration	mepivacaine	epinephrine > norepinephrine
Rabbit Guinea pig Rat Dog	Surface Infiltration Conduction	lidocaine	epinephrine > norepinephrine

Source: Lechat and Giroud (1971)

Sugar, added to decrease the duration of anesthesia by increasing the density of the local anesthetic solution injected into the spinal canal and thus limiting its diffusion towards the brain centers, has inactivated some local anesthetics. The activity of lidocaine in glucose, however, was not affected (Lechat and Giroud, 1971).

In the presence of carbon dioxide, the activity of solutions of lidocaine and mepivacaine was increased. In carbonated solutions of the bases of the two local anesthetics, it was found to be one-third of the induction of their chlorhydrates (Lechat and Giroud, 1971).

The addition of polymers to local anesthetics delayed the diffusion of local anesthetics and therefore increased their duration of action. Lidocaine hydrochloride with glucose, dextran, and epinephrine significantly increased infiltration anesthesia in humans (Lechat and Giroud, 1971).

In the presence of the cholinergic substance pyridostigmine, the anesthetic effect of lidocaine was increased in surface anesthesia. The activity of the drug was also increased in surface, infiltration, and conduction anesthesia with the prior parenteral administration of the antidepressants imipramine and amitriptyline (Lechat and Giroud, 1971).

In seven mongrel dogs, i.v. lidocaine (0.01, 0.1, 1.0, and 10 mg/kg) was observed to worsen bronchoconstriction induced by histamine by reducing plasma catecholamine concentrations. At doses of 1.0 and 10 mg/kg the histamine-decreased bronchial cross-sectional area was significantly reduced from 69.7% to 59.8% and 34.3%, respectively, while plasma concentrations of epinephrine and norepinephrine were decreased with 10 mg/kg (Hirota et al., 1999).

In a cross-over study design using human volunteers (4 female and 5 male, aged 21 to 25 years), pretreatment with erythromycin and itraconazole, inhibitors of CYP3A4, significantly increased peak plasma concentrations and the area under the lidocaine plasma concentration-time curve [AUC(0-∞)] of oral lidocaine (1 mg/kg). Erythromycin increased peak concentrations by 40% and the AUC (0-∞) by almost 50%; itraconazole increased each by 55% and almost 75%, respectively. Additionally, both chemicals increased the elimination half-life of lidocaine (Isohanni et al., 1999).

Section 10.3 provides a case of coinfusion of bupivacaine with pipecolylxylidine (PPX) in rats.

9.2 Reproductive and Teratological Effects

9.2.1 Bupivacaine

The details of the following studies are presented in **Table 29**.

When administered *in vitro* for 30 minutes to mouse oocytes, bupivacaine (0.01-100 µg/mL) caused fertilization and embryo developmental effects only at the highest concentration (Schnell et al., 1992; cited by Rice, 1994).

In rhesus monkeys, no neonatal neurobehavioral effects of bupivacaine were observed. In cognitive testing, relatively low performance levels were attained in the bupivacaine infants. Although group means for performance measures were generally higher in treated infants than controls, one infant showed a very low level of vigilance in the continuous performance test (<10%). During the visual novelty preference test, infants directed more, shorter fixations at visual stimuli. Furthermore, observation of behavior maturation patterns showed that the increase in manipulatory activity that normally occurs at two months of age was delayed in bupivacaine-exposed infants, while the increase in motor disturbance behaviors that normally occur at ten months of age was prolonged (Golub and Germann, 1998).

9.2.2 Lidocaine

When pregnant rats were treated continuously with lidocaine in doses one to five times the i.v. human dose or with single daily doses equivalent to the total daily i.v. infusion human dose no teratogenic effects were observed in the offspring (Fujinaga and Mazze, 1986; Ramazzotto et al., 1985; both cited by TERIS, 1997a). However, when given as single injections

in doses one to two times those used hourly in humans, lidocaine resulted in neonatal behavioral changes in the offspring (Smith et al., 1986; cited by TERIS, 1997a).

In pregnant mice, single injections of lidocaine in doses 50 to 70% of the daily human infusion dose produced increased frequencies of CNS anomalies in the embryos; these anomalies, however, were observed before embryogenesis was complete and therefore may not have resulted in malformations at birth (Martin and Jurand, 1992; cited by TERIS, 1997a). When mice were treated with daily i.p. injections in doses equivalent to those used for regional block in women undergoing follicular aspiration immediately following fertilization, delayed embryonic development occurred (del Valle and Orihuela, 1996; cited by TERIS, 1997a).

When given to baboons and sheep late in pregnancy, lidocaine produced changes in perinatal adaptation (Morishima et al., 1979, 1981, 1989; cited by TERIS, 1997a).

9.2.3 Other Amide Local Anesthetics

In the offspring of pregnant rats and rabbits treated with up to two times the maximum recommended human dose, etidocaine produced no teratogenic effects (USP DI, 1998; cited by TERIS, 1998). Prilocaine in doses up to three times the maximum human dose produced no adverse effects (USP DI, 1997; cited by TERIS, 1997b). In rats injected with the highest recommended mepivacaine human dose (6 mg/kg) on day 11 of pregnancy, significant abnormalities in behavioral test performance were observed in the offspring (Smith et al., 1986; cited by REPROTOX, 1999, and Shepard, 1999b).

No teratological studies of the other remaining amide local anesthetics were available.

Table 29. Reproductive Toxicity and Teratology of Bupivacaine

Species, Strain, and Age	Number and Sex of Animals	Chemical Form and Purity	Route, Dose, and Duration	Observation Period	Results/Comments	Reference
Mouse oocytes, Swiss Webster, ages n.p.	n.p.	bupivacaine, purity n.p.	*in vitro*; 0.01-100 µg/mL for 30 min	24, 48, and 72 hr	Effects of fertilization and embryo development were observed at the highest concentration.	Schnell et al. (1992; cited by Rice, 1994)
Monkey dams, rhesus (*Macaca mulatta*), ~9-yr-old [Dams were time bred.]	number of dams n.p. 11 infants: 9 M, 2 F	bupivacaine hydrochloride, purity n.p.	epidural catheter infusion; 0.60 mg/kg (0.5% test compound) for the initial 2-min period followed by 0.60 mg/kg over the next 20-min period at term (i.e., gestation day 165)	1 yr	Maternal plasma levels of bupivacaine at the end of infusion were 762 ng/mL (mean value). When bupivacaine was given during induced labor, maternal and fetal plasma levels at birth were 85 and 6 ng/mL, respectively, when delivery occurred 2 hr 15 min following infusion, and 1375 and 10 ng/mL when delivery occurred 30 min after infusion. Neonatal behavioral effects of bupivacaine were not seen. In *cognitive testing*, two bupivacaine infants failed to reach criterion on the delayed nonmatch-to-sample task (7.4-10.5 mo of age); one infant did not reach criterion on the object permanence test (1.5-3.5 mo of age); two failed to complete all four reversals in the discrimination reversal test (3.8-7.4 mo of age); and one infant showed a very low level of vigilance in the continuous performance test (<10%) (10.5-12 mo of age). During the novelty preference test, infants showed a stronger novelty preference with shorter fixations than controls (1.0-1.5 mo of age).	Golub and Germann (1998)

Table 29. Reproductive Toxicity and Teratology of Bupivacaine (Continued)

Species, Strain, and Age	Number and Sex of Animals	Chemical Form and Purity	Route, Dose, and Duration	Observation Period	Results/Comments	Reference
Monkey dams, rhesus (*Macaca mulatta*), ~9-yr-old [Dams were time bred.]	number of dams n.p. 11 infants: 9 M, 2 F	bupivacaine hydrochloride, purity n.p.	epidural catheter infusion; 0.60 mg/kg (0.5% test compound) for the initial 2-min period followed by 0.60 mg/kg over the next 20-min period at term (i.e., gestation day 165)	1 yr	In tests of *fine motor maturation* (1-3.5 mo of age), two infants failed to reach criterion for voluntary grasp, and one of these also failed to reach criterion for finger-thumb coordination. For the 1-14 wk observation period of *spontaneous behavior*, the percentage mature behaviors and percentage active behaviors were lower in infants than controls. For the 6-12 mo period, percentage active behaviors was greater for bupivacaine infants than controls, and disturbance behavior showed a distinct developmental time course.	Golub and Germann (1998) continued

Abbreviations: bw = body weight; F = females; hr = hour(s); M = males; min = minute(s); mo = month(s); n = number; n.p. = not provided; wk = week(s); yr = year(s)

9.3 Carcinogenicity

9.3.1 Bupivacaine

No studies were available.

9.3.2 Lidocaine

In a U.S. case-control study, one of 361 brain tumor cases had an association with lidocaine. Brain tumors were not found in controls matched by age, sex, and mother's racial/ethnic heritage. Controls were selected primarily by random-digit dialing. The overall incidences of brain tumors in the 21 cases exposed to nitrosatable drugs and the 55 controls corresponded to 6% and 5% of the cases and controls, respectively. The authors tentatively concluded that no increased risk of cancer could be ascribed to prenatal exposure to nitrosatable drugs based on this study (Carozza et al., 1995).

9.3.3 Other Amide Local Anesthetics

No studies were available.

9.4 Initiation/Promotion Studies

No studies were available.

9.5 Anticarcinogenicity

No *in vivo* studies were identified. Several studies evaluated cytotoxicity and inhibitory effects *in vitro*, which are discussed in Section 9.10.1.

9.6 Genotoxicity

9.6.1 Bupivacaine

No studies were available.

9.6.2 Lidocaine

In the absence of metabolic activation (S9), lidocaine (dose not provided) was negative in the *Escherichia coli* DNA-polymerase-deficient assay system (Rosenkranz and Leifer, 1980). In UV-irradiated cells of *E. coli*, lidocaine (dose notprovided) inhibited the excision-repair process.

In strains H/r30 (wild-type for DNA repair) and NG30 (recA$^-$ mutant), it almost completely inhibited the liquid-holding recovery and almost completely reduced the survival with time of liquid holding. Lidocaine had no effect on survival and mutation in strain Hs30 (uvrB$^-$ mutant) and no killing effect on unirradiated cells (Todo and Yonei, 1983).

In the presence and absence of S9, lidocaine (8 mg/plate) was not mutagenic in *Salmonella typhimurium* strains TA98 and TA100 (Waskell, 1978). However, when the study was reviewed by the *Salmonella* Work Group for the U.S. EPA's Gene-Tox program, the mutagenicity of the drug was determined to be inconclusive (Kier et al., 1986).

Exposure of intact cultured murine L1210 cells to lidocaine (8 mM) resulted in no significant DNA damage compared to untreated control cells. However, addition of lidocaine to bleomycin (BLM) A_2-pretreated cells significantly increased DNA breakage by 4.4-fold, whereas the addition of BLM A_2 to lidocaine-pretreated cells caused no increase in breakage (Lazo et al., 1985).

9.6.3 Other Amide Local Anesthetics

No studies were available.

9.7 Cogenotoxicity

No studies were available.

9.8 Antigenotoxicity

No studies were available.

9.9 Immunotoxicity

No studies were available.

9.10 Other Data

9.10.1 Cytotoxicity

9.10.1.1 Bupivacaine

In human M14 melanoma cells, treatment for two hours with bupivacaine hydrochloride (1.8 mM) reduced cell survival by 50%. The combination of heat (41-45 °C) and bupivacaine

was strongly synergistic. A two-hour combination treatment with a temperature of 37 °C, which inhibited clonogenic activity by 50%, lowered ATP content by 86% but increased ADP and AMP content, and decreased the adenylated energy. Bupivacaine was found to stimulate the basal rate of lactate production by 42%. Incubated with cells at either 37 or 42 °C for 50 minutes, the compound produced higher amounts of lactate than with heat alone. When cells were exposed to 0.8 mM bupivacaine for up to 30 minutes, the cellular content of bupivacaine was greater at 42 °C than at 37 °C. Treatment of cells at 37 °C with 1.8 mM bupivacaine caused changes in mitochondrial structure, the inner membrane, and the matrix, whereas cells heated at 42 °C for 50 minutes with 0.8 mM bupivacaine resembled untreated cells (Bruno et al., 1998).

9.10.1.2 Lidocaine

In mouse epidermal cells, lidocaine (1 mM) was an effective inhibitor of ornithine decarboxylase (ODC) induction by 12-*O*-tetradecanoylphorbol-13-acetate (TPA) and ultraviolet light (UV). Cells treated during and after TPA or after UV resulted in differential effects of 7% of TPA control and 18% of UV control (Yuspa et al., 1980).

In MO cells (an epithelioid-type C3H mouse embryo cell line), lidocaine (1, 10, and 100 µg/mL) did not produce multinucleation (De Brabander et al., 1976).

When cultured murine L1210 cells were incubated for one hour with lidocaine (0.1-10 mM), no decrease in clonogenicity occurred. However, addition of lidocaine to cells incubated with BLM A_2, which decreased clonogenicity to 43% of untreated control cells, caused a concentration-dependent potentiation of the BLM A_2 cytotoxicity. A combination of 10 µM BLM A_2 and 8 mM lidocaine caused a 1000-fold increase in cell kill compared with the use of the antitumor agent alone; with 30 µM BLM A_2, lidocaine increased cytotoxicity by more than 8000-fold. Significant potentiation of BLM A_2 cytotoxicity was observed to occur only with the simultaneous use of the compounds or when lidocaine was immediately added after BLM A_2 exposure. In addition, lidocaine (8 mM) reduced the total amount of cell-associated radioactivity by 57% compared to that seen only with incubation of [^{3}H]BLM A_2 (1 µM). Potentiation was not specific for the *C*- and *N*-terminus moieties of BLM; lidocaine (8 mM) enhanced cytotoxicity with 1, 10, and 20 µM BLM dA_2 (Lazo et al., 1985).

Lidocaine also increased BLM A_2 cytotoxicity toward human head and neck squamous carcinoma cells (A-253); a combination of 0.7 µM BLM A_2 and 8 mM lidocaine produced

14.3% of untreated control cells, while BLM A_2 alone produced 33.3% of untreated control (Lazo et al., 1985).

9.10.1.3 Prilocaine

When human osteoblastic Saos-2 cells were exposed for 48 hours to prilocaine (up to 10 mM), cell viability was decreased in a dose- and time-dependent manner. Co-incubation with cycloheximide, however, increased the cell viability of the treated cells in a dose-dependent fashion; cell death was up to three times lower than that of the prilocaine-only treated cells (Nakamura et al., 1999).

9.10.2 Ropivacaine Effect on the Energy Metabolism of Ehrlich Ascites Tumor Cells

In the absence and presence of hydrophobic anion tetraphenylboron (TPB^-), ropivacaine (up to 3.5 mM) inhibited the rate of oxygen consumption of Ehrlich ascites tumor cells. Ropivacaine (2 mM) alone also partially reactivated oligomycin-inhibited respiration in the cells, but addition of TPB^- lowered the rate of oxygen uptake to a level close to that with oligomycin alone. In addition, low concentrations of ropivacaine were significantly effective in reducing oxygen consumption on uncoupled respiration of the cells. In the absence of TPB^-, the uptake was inhibited by 86% with 3.5 mM ropivacaine; in the presence of TPB^-, a lower concentration, 1 mM ropivacaine, inhibited the rate by 85% (Di Padova et al., 1998).

Ropivacaine also improved total lactate production. In the absence of TPB^-, ropivacaine produced no changes in the rate of lactate production up to 1 mM; the maximum was reached at 3 mM and remained level. In contrast, in the presence of TPB^-, ropivacaine immediately raised the rate; the maximum was reached at 2 mM and remained almost constant (Di Padova et al., 1985).

Additionally, ropivacaine decreased the total adenine nucleotide content by 50%, with the largest effect on ATP, and depending on the concentration, decreased or collapsed mitochondrial membrane potential within Ehrlich ascites tumor cells (Di Padova et al., 1998).

9.10.3 Porphyria

The following amide local anesthetics have been classified as unsafe for use in acute porphyria: etidocaine, lidocaine, mepivacaine, prilocaine, and pyrrocaine (Moore, 1999).

10.0 STRUCTURE-ACTIVITY RELATIONSHIPS

This section reviews the toxicity of several metabolites of the amide local anesthetics, including trimecaine (metabolite mesidine).

10.1 Mesidine (2,4,6-Trimethylaniline)

Mesidine is a structural analogue of 2,6-xylidine (2,6-dimethylaniline).

Acute toxicity: In male Osborne-Mendel rats, an oral LD_{50} value of 660 mg/kg was obtained for mesidine as the hydrochloride (Lindstrom et al., 1969).

Subchronic exposure: In weanling Osborne-Mendel rats fed dietary levels of 100, 375, 750, and 1000 ppm mesidine hydrochloride for six months, three animals died. Growth inhibition and a dose-dependent increase in the mean liver weights were seen at all concentrations. In addition, kidney weights were increased moderately, and heart rates in males increased slightly. Significant increases in the testes mean weights were also observed. All rats showed significant pathological changes in the liver. There was a marked proliferation of bile ducts with some areas of fibrosis. At one of the high doses, livers showed a slight to moderate degree of fatty metamorphosis (Lindstrom et al., 1969).

When a maximum tolerated dose of mesidine hydrochloride (10.0 mg) was given by injection into the femoral vein of the rats, maximum methemoglobin formation was observed at 30 minutes (Lindstrom et al., 1969).

Carcinogenicity: When administered to 50 male Sprague-Dawley rats for two years in the diet, mesidine (doses not provided) produced hepatomas, seven cholangiocarcinomas, and severe cirrhosis of the liver (Russfield et al., 1973 abstr.).

Genotoxicity: In six male $B6C3F_1$ mice, a single i.p. injection of mesidine (150 and 300 mg/kg body weight) given 16 hours before being sacrificed produced DNA damage in the liver cells (Przybojewska, 1999). The compound has also been found to damage bone marrow cells of the animals (Przybojewska, 1997; cited by Przybojewska, 1999). In the absence of activation,

mesidine was mutagenic in *S. typhimurium* and was positive for DNA repair in Chinese hamster hepatocytes (Yoshimi et al., 1988; cited by Przybojewska, 1999).

10.2 Pipecolic Acid

Pipecolic acid is a metabolite of bupivacaine, mepivacaine, and ropivacaine.

Acute toxicity: In adult NMRI male mice (10 per dose), i.p. injection of pipecolic acid (200, 400, or 800 mg/kg) in saline produced a mean convulsant activity of 0%. The acute induced mortality was 0, 30, and 60%, respectively, with increasing dosage, and an LD_{50} value of 610 mg/kg was calculated (Bruguerolle et al., 1994).

Genotoxicity: In a direct bacterial assay using *S. typhimurium* strains TA1530, TA1531, TA1532, and TA1964, pipecolic acid (1-5 mg) was not mutagenic. In a microsomal mutagenesis assay using the same strains, the compound (0.005, 0.05, 0.15, and 0.50 M) also gave a negative result. At >0.15 M, pipecolic acid was toxic to the bacteria; the percent survival at 0.5 M was 28%. In a host-mediated assay using male C3H/HeJ mice, it (600 mg/kg) was not mutagenic in *S. typhimurium* strains TA1534, TA1950, TA1951, and TA1952 (Green and Savage, 1978).

10.3 Pipecolylxylidine (PPX)

Pipecolylxylidine (PPX) is a metabolite of bupivacaine, mepivacaine, and ropivacaine.

Acute toxicity: In adult NMRI male mice (10 per dose), i.p. injection of PPX (100, 112.5, 125, 150, 200 or 400 mg/kg) in saline resulted in mean convulsant activities of 0, 10, 80, 60, 90, and 100%, respectively. The times required to convulse were 230±30, 270±24, 255±21, 442±84, and 418±32 seconds for 200, 150, 125, 112.5, and 100 mg/kg, respectively. An i.p. LD_{50} value of 140 mg/kg was calculated (Bruguerolle et al., 1994).

In ten male Sprague-Dawley rats, i.v. infusion of PPX (4 mg/kg/min) until asystole produced seizure activity in one animal almost two minutes after the first appearance of arrhythmia. In the remaining rats, subcortical seizure activity but no cortical involvement was seen. The mean doses of the compound causing arrhythmia and asystole were 24 and 48 mg/kg, respectively. The decrease in arterial blood pressure was greater than that from bupivacaine

alone. In addition, the plasma concentrations of PPX measured at five minutes were somewhat slightly higher than the bupivacaine concentration (Rosenberg and Heavner, 1992).

When PPX (0.67 mg/kg/min) was coinfused with bupivacaine (2 mg/kg/min) in six rats, a potentiation of the cardiac toxicity of the latter compound was observed; there was a significant decrease in the doses causing arrhythmia and asystole. Furthermore, the decrease in the heart rate was greater than using either compound alone; two of six animals experienced cardiovascular collapse within five minutes (Rosenber and Heaver, 1992).

10.4 *o*-Toluidine

o-Toluidine (2-methylaniline) is a metabolite of prilocaine.

Acute toxicity: In male Sprague-Dawley rats, the oral LD_{50} was 900 mg/kg body weight for undiluted *o*-toluidine. In mice, rats, and rabbits, the values were 515, 670, and 843 mg/kg body weight, respectively (IARC, 1978, 1982). In male Osborne-Mendel rats, an oral LD_{50} value of 2951 mg/kg was obtained for *o*-toluidine as the hydrochloride (Lindstrom et al., 1969).

When applied to the skin of rabbits, *o*-toluidine (10 or 500 mg) for 24 hours, unoccluded, mild irritation was observed. However, on the eyes, the compound (750 µg) for 24 hours produced severe irritation (RTECS, 1999). In males, the LD_{50} was 3250 mg/kg body weight (IARC, 1978, 1982).

Short-term exposure: When fed daily to rats for 5, 10, and 20 days, *o*-toluidine (doses not provided) produced splenic congestion, increased hematopoiesis, and hemosiderosis with bone marrow hyperplasia (Hiles and Abdo, 1990). When fed to male and female albino rats in initials doses of 2 g and then 1 g after 64 days for 91 days, epithelial changes in the bladder, including keratosis, metaplasia, and a tendency for papillomatosis were observed (IARC, 1978). Other effects seen in rats were methemoglobinemia, reticulocytosis, and anemia, while in mice, methemoglobinemia was observed (IARC, 1982). In cats and dogs, the compound also increased methemoglobin (Hiles and Abdo, 1990).

In $B6C3F_1$ mice and Fischer 344 rats of both sexes fed diets containing up to 50,000 mg/kg *o*-toluidine hydrochloride for seven weeks, a dose-dependent reduction in mean body

weight gain was observed. The spleens of rats had pigment deposition at the highest dose, while in mice renal and splenic pigmentation were seen at 12,500 mg/kg (IARC, 1982).

Chronic exposure: When administered in the feed to 50 male and 50 female F344 rats and B6C3F_1 mice, *o*-toluidine hydrochloride (3000 or 6000 ppm for the former and 1000 or 6000 ppm for the latter) for 101 to 104 weeks produced lower mean body weights that were dose-related compared to untreated animals (controls). In rats, mortality was also dose-related (NTP, 1979).

Reproductive and teratological effects: *o*-Toluidine (doses not provided) applied to the skin of rats had paternal, maternal, and newborn effects. Adverse effects on spermatogenesis were seen in males. Maternal effects included those of the ovaries and fallopian tubes and changes or disorders in the menstrual cycle. Physical effects and effects on growth statistics (e.g., reduced weight gain) were seen in newborns (RTECS, 1999).

When applied on the gonads of albino female rats for four months, *o*-toluidine (doses not provided) affected the ovarian cycle, ovary morphostructure, reproductive capability, and the offspring. In male rats, stimulated spermatogenesis was observed (Hiles and Abdo, 1990).

Carcinogenicity: When fed to rats for 91 days, *o*-toluidine (doses not provided) caused epithelial changes in the bladder such as keratosis, metaplasia, and the tendency to beginning papillomatosis. Subcutaneous injections of the compound for over 397 days produced hyperplasia of the basal cells in the Zymbal glands of rats (Hiles and Abdo, 1990). When administered to 50 male Sprague-Dawley rats for two years in the diet, *o*-toluidine produced hepatomas. In 83% of the animals, s.c. fibromas or fibrosarcomas were found (Russfield et al., 1973 abstr.).

When administered in the feed to 50 male and 50 female F344 rats, *o*-toluidine hydrochloride (3000 or 6000 ppm) for 101 to 104 weeks produced several types of sarcomas of the spleen and other organs in both sexes. Mesotheliomas of the abdominal cavity or scrotum and an increased incidence of fibromas of the s.c. tissue occurred in males, while transitional-cell carcinomas of the urinary bladder and an increased incidence of fibroadenomas or adenomas of the mammary gland were observed in females (NTP, 1979, 1998).

When administered in the feed to 50 male and 50 female B6C3F$_1$ mice, *o*-toluidine hydrochloride (1000 or 3000 ppm) produced hemangiosarcomas at multiple sites in males and hepatocellular carcinomas or adenomas in females (NTP, 1979). In another strain (not specified), hemangiosarcomas and hemangiomas of the abdominal viscera in both sexes were reported (NTP, 1998). In male and female Charles River (HA/ICR) CG-1 mice, the compound at two dose levels in the diet produced vascular tumors (IARC, 1978, 1982, 1987).

Subcutaneous injections of *o*-toluidine (doses not provided) in the hamster have produced no cancer (Hiles and Abdo, 1990). In rabbits and guinea pigs injected s.c. with *o*-toluidine (2% solution; 1.0 and 1.5 mL, respectively) six times per week, papillomas in the bladder were observed (IARC, 1978, 1982, 1987).

Genotoxicity: Studies with *o*-toluidine have produced equivocal results. The overall conclusion regarding the mutagenicity of the compound was "nondefinitive" by the *Salmonella* Work Group for the U.S. EPA's Gene-Tox Program (Kier et al., 1986).

Only in the presence of metabolic activation (S9) did *in vitro* studies give positive results (Hiles and Abdo, 1990). It was negative in the *Salmonella* mutagenicity assay, but positive in the standard pol A assay with enzyme and in the modified pol A assay without enzyme (Rosenkranz and Leifer, 1980). No reverse mutations were induced in *S. typhimurium* strains TA98, TA100, TA1535, TA1537, or TA1538 in the presence or absence of S9 with concentrations up to 1000 µg/plate. However, the mutations were induced in *S. typhimurium* strain TA98 in the presence of both norharman and a rat S9 induced by polychlorinated biphenyls. When tested in V79 Chinese hamster cells incubated with *o*-toluidine (0.3-10 mM) for two hours in the presence of Aroclor-induced rat liver microsomes, no single-strand DNA breaks were observed (IARC, 1978, 1982). In *Drosophila* somatic mutation occurred, while in yeast *o*-toluidine induced aneuploidy but not mitotic recombination (IARC, 1987).

RTECS (1999) and EMIC (1999) provide numerous results of various tests.

10.5 2,6-Xylidine

2,6-Xylidine is a potential or known metabolite of bupivacaine, etidocaine, lidocaine, mepivacaine, pyrrocaine, and ropivacaine.

Acute toxicity: In male Osborne-Mendel rats, an oral LD_{50} value of 2042 mg/kg was obtained for 2,6-xylidine as the hydrochloride (Lindstrom et al., 1969). In male Sprague-Dawley rats and CF_1 mice, the oral LD_{50} values were 1230 mg/kg and 710 mg/kg, respectively. For Fischer 344 rats administered 2,6-xylidine by gavage and without a vehicle, the LD_{50} was 630 mg/kg. For females given the compound by gavage in corn oil, the LD_{50} was 1160 mg/kg. For male and female Charles River CD rats, LD_{50} values between 1270 and 1310 mg/kg were reported. Additionally, an i.v. dose of 2,6-xylidine (30 mg/kg body weight) in a pH 5.5 saline vehicle produced methemoglobinemia in cats but not dogs (IARC, 1993).

Short-term exposure: In female and male weanling Osborne-Mendel rats fed 2,6-xylidine (as the pure hydrochloride in dietary levels of 375, 750, 2500, 5000, and 10,000 ppm) for three or six months, growth inhibition was observed; almost 25% weight retardation was reached at the highest dose. Red blood cell changes toward target cell anemia were also less pronounced at all levels. The liver and kidney showed the most dramatic weight and pathological changes, particularly at 26 weeks. With 10,000 ppm the kidneys showed a slight to moderate degree of irregular pitting or depressed scarring. In addition, slight chronic congestion was found in the spleens and pneumonia, ovarian cysts, or distented uterine horns were occasionally seen in the animals (Lindstrom et al., 1963).

In male Fischer 344 rats given 2,6-xylidine (157.5 mg/kg body weight) daily by gavage for five to 20 days, splenic hemosiderosis was seen. In male and female Sprague-Dawley rats, the compound (400-700 mg/kg) given daily by gavage for one month, decreased weight gain, lowered hemoglobin values, liver enlargement, and increases in microsomal glucuronyltransferase levels occurred in both sexes, while increases in aniline hydroxylase levels occurred only in females. When administered to female and male Fischer 344 rats, the compound (up to 310 mg/kg) five days per week for 13 weeks increased liver weight but decreased body weight and erythrocyte, hemoglobin, and hematocrit levels. In male and female beagle dogs, oral doses of 2,6-xylidine (50 mg/kg body weight) for one month produced decreased body weight, hyperbilirubinemia, hypoproteinemia, and significant fatty degenerative changes in the liver (IARC, 1993).

Chronic exposure: When 56 male and 56 female Charles River CD rats, offspring of animals given diets containing 2,6-xylidine (300, 1000, or 3000 ppm) before breeding, during pregnancy, and through the lactation period for 104 weeks, a reduction in body weight gain was observed in the high-dose male and female rats. Survival was also reduced but only in the mid- and high-dose males. Survival was high for all groups of females but only during the second year of the study (NTP, 1990).

Carcinogenicity: In a two-year carcinogenic study, doses of 2,6-xylidine (300, 1000, or 3000 ppm) in the feed produced papillary adenomas and carcinomas of the nasal cavity in 56 female and 56 male Charles River CD rats. At the highest dose, carcinomas and adenocarcinomas occurred in 28 males and 24 females, and papillary adenomas were found in 10 males and 6 females. Malignant mesenchymal tumors were also found in the nasal cavity. Rhabdomyosarcomas were found in two males and two females, all of the high-dose group, and an undifferentiated sarcoma was observed in one female rat. The nonneoplastic lesions of the cavity included acute inflammation, epithelial hyperplasia, and squamous metaplasia. Increased incidences of s.c. tissue fibromas, which were dose-related, occurred in high-dose females and males, as well as s.c. fibrosarcomas. Additionally, there was a significant dose-related increase in the incidence of female rats with neoplastic nodules of the liver, and metastatis to the brain was seen in five males and seven females of the high-dose group (NTP, 1990; IARC, 1993).

In male and female rats, daily doses of 150 mg/kg 2,6-xylidine produced carcinomas and adenomas of the nasal cavity. As with the higher doses in the NTP study, rhabdomyosarcomas were also observed in the nasal cavity of both sexes, s.c. fibromas and/or fibrosarcomas were found in both male and female rats, and neoplastic nodules of the liver were seen only in the female rats (Noven, 1997).

Genotoxicity: The genotoxicity of 2,6-xylidine in *S. typhimurium* have been conflicting. Some studies have shown weak activity in the presence of an exogenous metabolic system from the liver of hamster, but not that of the rat (IARC, 1993). Under metabolic activation, 2,6-xylidine was found to be weakly mutagenic in the Ames test. In the absence of metabolic activation, it produced mutation in *S. typhimurium*. In *E. coli* phage inhibition capacity (39 µg/well) was

observed, and in hamster ovary cells cytogenic analysis (1 g/L) and sister chromatid exchanges (301 mg/L) were seen (RTECS, 1999).

With or without activation, it was mutagenic at the thymidine kinase locus of mouse lymphoma cells, inducing chromosome aberrations and sister chromatid exchanges at concentrations ≥1.2 mg/mL. In contrast, 2,6-xylidine failed to induce unscheduled DNA synthesis in rat hepatocytes and micronuclei in the bone marrow of mice treated orally with the compound. In another *in vivo* assay it failed to induce chromosome damage in polychromatic erythrocytes or preferential killing of DNA repair-deficient bacteria in liver, lung, kidney, testes, and blood extracts from mice. Its ability to covalently bind to DNA of ethmoid turbinates and liver of rats after oral pretreatment, however, indicates that 2,6-xylidine may be genotoxic under certain conditions (IARC, 1993; Noven, 1997).

EMIC (1999) provides data on the effects of 2,6-xylidine on nucleic acids (e.g., phage induction, DNA binding, DNA-repair-UDS, and single-strand DNA breaks), on gene mutations (e.g., Ames test and recessive lethal-sex linked) induced by the compound, and the results of other genotoxicity studies.

11.0 ONLINE DATABASES AND SECONDARY REFERENCES

11.1 Online Databases

Chemical Information System Files

SANSS (Structure and Nomenclature Search System)
TSCATS (Toxic Substances Control Act Test Submissions)

DIALOG Files

Kirk-Othmer Encyclopedia of Chemical Technology

National Library of Medicine Databases

EMIC and EMICBACK (Environmental Mutagen Information Center)

STN International Files

BIOSIS
EMBASE
MEDLINE
TOXLINE

TOXLINE includes the following subfiles:

Toxicity Bibliography	TOXBIB
International Labor Office	CIS
Hazardous Materials Technical Center	HMTC
Environmental Mutagen Information Center File	EMIC
Environmental Teratology Information Center File (continued after 1989 by DART)	ETIC
Toxicology Document and Data Depository	NTIS
Toxicological Research Projects	CRISP
NIOSHTIC®	NIOSH
Pesticides Abstracts	PESTAB
Poisonous Plants Bibliography	PPBIB
Aneuploidy	ANEUPL
Epidemiology Information System	EPIDEM
Toxic Substances Control Act Test Submissions	TSCATS
Toxicological Aspects of Environmental Health	BIOSIS
International Pharmaceutical Abstracts	IPA
Federal Research in Progress	FEDRIP
Developmental and Reproductive Toxicology	DART

Databases Available on the Internet

Phytochemeco Database (Agricultural Research Service)

In-House Databases

CPI Electronic Publishing Federal Databases on CD
Current Contents on Diskette®
The Merck Index, 1996, on CD-ROM

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APPENDIX A

Metabolism and Pharmacokinetics of Bupivacaine

APPENDIX A

This appendix contains the details of studies of the metabolism and pharmacokinetics of bupivacaine. The metabolites and proposed metabolites of bupivacaine are listed in the compounds measured column of **Table A-1**. A key to the codes used for the metabolites of bupivacaine is given below along with the organization of Appendix A.

Key to Chemical Compounds Detected or Proposed as Metabolites of Bupivacaine

Code	Chemical Compound	Code	Chemical Compound
BUP	Bupivacaine	(*R*)-4'-PPXOH	(2*R*)-4'-Hydroxypipecolo-2',6'-xylidide
(–)-BUP	(*S*)-Bupivacaine	(*S*)-4'-PPXOH	(2*S*)-4'- Hydroxypipecolo-2',6'-xylidide
(+)-BUP	(*R*)-Bupivacaine	3'-BUPOH	3'-Hydroxybupivacaine
PPX	Pipecolo-2',6'-xylidide; Desbutylbupivacaine; Pipecoloxylidide	4'-BUPOH	4'-Hydroxybupivacaine
(*R*)-PPX	(*R*)-Pipecolo-2',6'-xylidide; (*R*)-Desbutylbupivacaine; (*R*)-Pipecoloxylidide	BUPOH	Hydroxybupivacaine; Monohydroxylated derivative on the piperidine ring [unspecified attachment for hydroxyl group]
(*S*)-PPX	(*S*)-Pipecolo-2',6'-xylidide; (*S*)-Desbutylbupivacaine; (*S*)-Pipecoloxylidide	□-BUPOH	*N*-(2,6-Dimethylphenyl)-1-(2-hydroxybutyl)-2-piperidinecarboxamide
3'-PPXOH	3'- Hydroxypipecolo-2',6'-xylidide	*N*-Bu-PIPamide*	*N*-Butylpipecolyl-2-amide; 1-Butyl-2-piperidinecarboxamide; *N*-Butylpiperidine-2-carboxylic acid amide
(*R*)-3'-PPXOH	(2*R*)-3'- Hydroxypipecolo-2',6'-xylidide	PrCHO*	Butyraldehyde
(*S*)-3'-PPXOH	(2*S*)-3'- Hydroxypipecolo-2',6'-xylidide	PIP	Pipecolic acid
4'-PPXOH	4'- Hydroxypipecolo-2',6'-xylidide	XYL*	2,6-Xylidine

* These compounds have been proposed as metabolites, but they have not been confirmed.

Table A-1. Metabolism Studies of Bupivacaine in Humans and Experimental Animals

Subjects	Dose	Compounds Measured[a]	Remarks	Reference
27 Pregnant Women	Epidural administration of 0.5% bupivacaine (82.1 ± 29.4 mg; n=27) and 2.0% lidocaine (183.3 ± 104.2 mg; n=22); 7 received fentanyl as well; 5 received general anesthesia	Determined bupivacaine [BUP], lidocaine [LID], and PPX [PPX] concentrations in maternal serum and breast milk. Serum and breast milk samples were taken 2, 6, and 12 hr after the beginning of local anesthetic infusion.	The concentrations of bupivacaine and lidocaine were highest in breast milk (0.09 ± 0.09 and 0.86 ± 0.79 □g/mL, respectively) and serum (0.23 ± 0.10 and 0.94 ± 0.54 □g/mL) 2 hr after infusion initiation. The milk/serum ratio was 0.36 for bupivacaine and 0.85 for lidocaine at 2 hr. The PPX concentration was highest in serum (0.17 ± 0.11 □g/mL) and breast milk (0.25 ± 0.20 □g/mL) 12 hr after infusion began. The milk/serum ratio was 1.52. Bupivacaine, lidocaine, and PPX are differentially excreted into breast milk. The relatively large amount of PPX excreted into milk should be considered since its CNS toxicity is twice that of bupivacaine (Bruguerolle et al., 1994). It was concluded that the concentrations of local anesthetics in breast milk were low (less than one part per million) and that breast feeding was safe after the use of local anesthetics.	Ortega et al. (1999)
3 Male Volunteers	i.v. dose of 40 mg racemic bupivacaine over an 8-min period	Bupivacaine [BUP] (0.29% of administered dose recovered in 24-hr urine collection) 3'-Hydroxybupivacaine [3'-BUPOH] (3.66%) 4'-Hydroxybupivacaine [4'-BUPOH] (1.71%)	This study was primarily for the evaluation of the use of capillary gas chromatography-selective ion monitoring mass spectrometry for the determination of bupivacaine metabolites. This was the only study reviewed that found higher concentrations of the 3'-hydroxy metabolite than of the 4'-hydroxy metabolite in humans.	Zhang et al. (1998)
3 Human Patients (Sex n.p.)	Epidural administration initial bolus of 75 mg bupivacaine followed by infusion with 7.5 mg/hr	The metabolites detected in urine were: Desbutylbupivacaine [PPX] 3'-Hydroxybupivacaine [3'-BUPOH] 4'-Hydroxybupivacaine [4'-BUPOH] *N*-Butylpipecolyl-2-amide [*N*-Bu-PIPamide] Unidentified monohydroxylated isomers on the piperidine ring [BUPOH]	There was no quantitation of the bupivacaine metabolites. Similar metabolites were found in humans as were found in rats (Dennhardt et al., 1978a); however, 4'-hydroxybupivacaine was not found in the rat, but was found in humans in this study.	Dennhardt and Konder (1980)

Table A-1. Metabolism Studies of Bupivacaine in Humans and Experimental Animals (Continued)

Subjects	Dose	Compounds Measured[a]	Remarks	Reference
11 Healthy Human Young Adult Males	i.v. infusion with 0.1% bupivacaine (12 mg bolus dose followed by infusion of 5, 10, or 15 □g/kg/min; totals: 199 ± 29 mg), urine was collected for 72 hr after infusion	Bupivacaine [BUP] (0.7%) Pipecoloxylidide [PPX] (4.8%)	After 45 min, blood plasma concentrations of bupivacaine ranged from 0.1 to 1.8 µg/mL. Analysis of the 72-hr urine collection revealed that 0.7% of the administered dose was excreted as bupivacaine and 4.8% was excreted as PPX. Bupivacaine (~0.7% of the administered dose) and PPX (~3.5%) were maximally excreted in the urine during the first 24-hr urine collections. The mean urinary pH was 6.1 ± 0.3. The concentrations of bupivacaine detected in the urine were comparable to concentrations reported by Reynolds (1971) and Eriksson and Granberg (1965). Urinary excretion of bupivacaine was pH-dependent, but excretion of PPX was not.	Friedman et al. (1982)
5 Male Patients	Epidural administration of a bolus dose of (±)-bupivacaine hydrochloride (0.5%v/v) followed by continuous epidural infusion with rac-bupivacaine fentanyl; total bupivacaine ranged from 840 to 2093 mg over 60-120 hr	Compounds detected in urine collected every 5.5 hr during infusion and for 24 hr post-infusion: (*R*)-3'-Hydroxybupivacaine [(*R*)-3'-BUPOH] (*R*)-4'-Hydroxybupivacaine [(*R*)-4'-BUPOH] (*R*)-Desbutylbupivacaine [(*R*)-PPX] (*R*)-Bupivacaine [(+)-BUP] (*S*)-Desbutylbupivacaine [(*S*)-PPX] (*S*)-3'-Hydroxybupivacaine [(*S*)-3'-BUPOH] (*S*)-4'-Hydroxybupivacaine [(*S*)-4'-BUPOH] (*S*)-Bupivacaine [(–)-BUP]	A mean 75% of the dose of bupivacaine was accounted for in the urine, ranging from 67.9 to 81.7% in the 5 patients. The total mass of the (*R*)-enantiomers recovered in urine accounted for 79.6 ± 6% of the (*R*)-enantiomer dose and only 71 ± 8% of the (*S*)-enantiomer dose was recovered. The rate of excretion of the stereoisomers of bupivacaine, 1.27 ± 0.26 mg/hr for (R)-enantiomers and 0.76 ± 0.13 mg/hr for (*S*)-enantiomers, and metabolites reached a steady state after 30 hr. The fraction of the enantiomer dose that was excreted in the urine unchanged ranged from 14.3% to 39.1% for (+)-(*R*)-bupivacaine and 9.2% to 14.0% for (–)-(S)-bupivacaine. The finding of a greater amount of the (R)-enantiomer being unchanged at steady state indicates that the ratio of renal to total clearance of (*R*)-bupivacaine is higher than that of the (*S*)-bupivacaine. In 3 patients *N*-dealkylation was the predominant route of metabolism and in 2 patients hydroxylation was the predominant route. Excretion was stereoselective for all metabolites except desbutylbupivacaine (PPX), which is a product of dealkylation. Regioselectivity and stereoselectivity are important factors in the metabolism of bupivacaine and they may vary from one patient to another. This study suggests that metabolism of bupivacaine may be mediated by different isoforms of cytochrome P450, each with different substrate selectivities.	Fawcett et al. (1999)

Table A-1. Metabolism Studies of Bupivacaine in Humans and Experimental Animals (Continued)

Subjects	Dose	Compounds Measured[a]	Remarks	Reference
5 Healthy Male Volunteers (age: 21 to 22 yr)	i.v. dose of bupivacaine (n = 3; 43.42 mg each) and PPX (n = 2; 43.12 mg); all doses were administered at different times so that no subject received more than one injection in one week	Determined the extent of PPX formation in plasma and excretion in urine after administration of bupivacaine and compared it to that after mepivacaine administration. Bupivacaine [BUP] (6% of dose found in 24-hr urine collection) Pipecoloxylidide [PPX] (5%)	After administration of bupivacaine, a 24-hr urine collection contained 2.61 ± 0.25 mg (6% of the dose) bupivacaine and 2.2 ± 0.32 mg (5%) PPX. When PPX was administered, half of the dose was excreted as PPX in the urine after 24 hours. Between 10 min and 2 hr following dosing, bupivacaine was eliminated from the blood more rapidly than mepivacaine; thereafter, the rates of elimination were similar. Since such small amounts of the doses of mepivacaine and bupivacaine were excreted as PPX, and 50% of the PPX dose was excreted unchanged, N-dealkylation was not as important for the metabolism of these two anesthetics as it was for lidocaine. N-Dealkylation of the anesthetics may be inhibited by steric interference from the piperidine ring. However, as noted by Fawcett et al. (1999) (see above) differences in metabolite concentrations may be due to enzyme differences among the subjects (in 3 of 5 male patients in their study, dealkylation to PPX predominated over hydroxylation).	Reynolds (1971)
Two Female Patients (receiving anesthesia for urinary bladder prolapse; age: both 67 yr)	Epidural administration of plain bupivacaine (1.5 mg/kg bw)	Determined desbutylbupivacaine [PPX] and 4'-hydroxybupivacaine [4'-BUPOH] concentrations in 3- to 6-hr urine and serum collections. Compounds detected and mean percentage of the administered dose in 24-hr urine collections were: Bupivacaine [BUP] (0.20%) Pipecoloxylidide [PPX] (1.21%) 4'-Hydroxybupivacaine [4'-BUPOH] (0.09%)	The limit of detection for the HPLC assay was 10 □g/L (0.01 mg/L). The concentration of bupivacaine peaked at 30 min in one patient (1.45 mg/L) and at 15 min in the other patient (0.46 mg/L). At 2 hr post-anesthesia, the bupivacaine concentrations in serum were 0.54 and 0.24 mg/L. At 24 hr post-anesthesia, bupivacaine concentrations in serum were 0.17 and 0.07 mg/L. PPX (desbutylbupivacaine) was first detected in serum in both patients 45 min after anesthesia and concentrations were 0.01 and <0.01 mg/L. In one patient, PPX concentrations in serum increased to 0.03 mg/L at 2 hr and remained at that level until the end of sampling (24 hr). PPX serum levels in the other patient never rose above 0.01 mg/L. 4'-Hydroxybupivacaine concentrations in serum were first detected at 45 min in one patient (0.01 mg/L) and at 2 hr in the other patient (0.02 mg/L). In the 24-hr urine collections, bupivacaine was excreted as 0.22% and 0.17% of the dose in the two women. In the 24-hr urine collections, PPX was excreted as 1.55% and 0.87% of the dose in the two women and 4'-hydroxybupivacaine was excreted as 0.11% and 0.07% of the dose.	Lindberg et al. (1986)

Table A-1. Metabolism Studies of Bupivacaine in Humans and Experimental Animals (Continued)

Subjects	Dose	Compounds Measured[a]	Remarks	Reference
6 Healthy Pregant Women undergoing an uncomplicated delivery (Group1, mean age: 27.0 yr)	Extradural administration with bupivacaine (1.78 mg/kg bw; mean total = 112.2 mg)	Compounds detected in 12-hour urine collection: Bupivacaine [BUP] (0.22% of the dose) *N*-Desbutylbupivacaine [PPX] (1.56%) 4'-Hydroxybupivacaine [4'-BUPOH] (0.67%)	Determined and compared the excretion of bupivacaine, desbutylbupivacaine, and 4'-hydroxybupivacaine among the three groups of women. The urine in the group of pregnant women was only collected for 12 hr compared with both 12 and 24 hr in the other 2 groups. The maximum concentration of bupivacaine in the serum was much higher in the pregnant women (1.39 ± 0.44 mg/L) than in the serum of women in group 2 or 3 (0.89 ± 0.28 and 0.84 ± 0.37 mg/L, respectively). The $T_{1/2}$ was lower in the younger nonpregnant women (11.90 ± 2.01 hr) than in pregnant women and older women (13.28 ± 1.02 and 14.83 ± 3.88 hr, respectively), but this was not significantly different statistically. The time to the maximum plasma concentration was similar in all groups (~ 24-25 min). The maximum concentration of PPX was also higher in the serum of the pregnant women at all times. At 24 hours after administration, the PPX concentrations in serum of the women in groups 1, 2, and 3 were approximately 0.15, 3.5, and 2.0 mg/L, respectively. There was no significant difference in the urinary excretion of bupivacaine or PPX among the three groups. All forms of bupivacaine and PPX found in the urine were unconjugated. No unconjugated 4'-hydroxybupivacaine was detected in the urine of pregnant women; however, in groups 2 and 3, 83.6 ± 8.8% and 88.1 ± 10.1% of the 4'-hydroxybupivacaine found in the urine was conjugated. It was noted that absorption from the extradural space may result in overestimation of the $T_{1/2}$ when compared to i.v. administration of bupivacaine (2-3 hr) (Tucker and Mather, 1979; Kanto, 1986). **The authors concluded that N-dealkylation and hydroxylation of bupivacaine were minor metabolic pathways, while the hydrolysis of the amide moiety deserves more investigation**. Pregnancy, not age, may affect the pharmacokinetics and metabolism of bupivacaine.	Pihlajamaki et al. (1990)
6 Healthy Female Patients <65 yr old (Group 2, mean age: 47.5 yr)	Extradural administration with bupivacaine (1.58 mg/kg bw; mean total = 99.4 mg)	Compounds detected in 12-hr and 24-hr urine collections: Bupivacaine [BUP] (0.04% and 0.13% of the dose) *N*-Desbutylbupivacaine [PPX] (0.32% and 1.53%) 4'-Hydroxybupivacaine [4'-BUPOH] (0.98% and 1.56%)		
6 Healthy Female Patients >65 yr old (Group 3, mean age: 74.0 yr)	Extradural administration with bupivacaine (1.50 mg/kg bw; mean total = 94.5 mg)	Compounds detected in 12-hr and 24-hr urine collections: Bupivacaine [BUP] (0.16% and 0.24% of the dose) *N*-Desbutylbupivacaine [PPX] (0.21% and 0.89%) 4'-Hydroxybupivacaine [4'-BUPOH] (0.66% and 1.28%)		

Table A-1. Metabolism Studies of Bupivacaine in Humans and Experimental Animals (Continued)

Subjects	Dose	Compounds Measured[a]	Remarks	Reference
6 Female Rhesus Monkeys	Single s.c. dose with 2 mg/kg of [pipecolyl-G-^{3}H]bupivacaine	Determined distribution, biotransformation, and excretion of bupivacaine in the monkey. Compounds found were: Bupivacaine (5.9% of the total dose) [BUP] Desbutylbupivacaine (3.8%) [PPX] 4'-Hydroxydesbutylbupivacaine (4.9%) [4'-PPXOH] 4'-Hydroxybupivacaine (8.0%) [4'-BUPOH] Pipecolic acid (51.7%) [PIP] * 2,6-xylidine was not mentioned as a metabolite but is likely since PIP was reported	Radioactivity was found in all tissues at all time periods. The highest amounts of radioactivity were found in the liver (14.2 nmol bupivacaine/g tissue), kidney (15.2 nmol/g), lung (8.2 nmol/g), and pancreas (6.9 nmol/g) 1 hr after dose administration. All radioactivity in all tissues examined was below 1 nmol/g tissue 24 hr after dose administration. The radioactivity present at the injection site was 21% of the dose 1 and 6 hr after administration but fell to 0.2% after 24 hr. The amount of radioactivity found in the intestinal contents was 5.8% of the dose 1 hr after administration, 1.6% after 6 hr, and less than 0.1% after 24 hr. After 24 hr, 79.9% of the dose was excreted in the urine and 6.0% in the feces. 3'-Hydroxybupivacaine was not detected in the urine of the monkey. About 8% of the dose was excreted as conjugated 4'-hydroxydesbutylbupivacaine and 4'-hydroxybupivacaine. Amide hydrolysis is the principal metabolic pathway in the monkey.	Goehl et al. (1973)
1 Rabbit (Strain and Sex n.p.)	i.v. injection, 8x/day each 80 min with 1.125 mL bupivacaine (5 mg/mL)	Compounds detected in urine were: 3'-Hydroxybupivacaine [3'-BUPOH] 4'-Hydroxybupivacaine [4'-BUPOH] 2-Hydroxybutylbupivacaine [□-BUPOH]	Urine was collected for 24 hours after initiation of infusion. The metabolites of bupivacaine were not quantitated.	Bouché and Lhoest (1976)

Table A-1. Metabolism Studies of Bupivacaine in Humans and Experimental Animals (Continued)

Subjects	Dose	Compounds Measured[a]	Remarks	Reference
Rats (Strain and Sex n.p.)	Intraduodenal continuous infusion with 0.5% bupivacaine (20 mg/kg in 3 mL) over 1 min	Compounds detected in urine were: Desbutylbupivacaine [PPX] 3'-Hydroxybupivacaine [3'-BUPOH] *N*-Butylpipecolyl-2-amide [N-Bu-PIPamide] 2 Monohydroxylated isomers on the piperidine ring [BUPOH]	Dennhardt and co-workers are the only authors who propose a metabolite in which the amino grpoup of 2,6-xylidine is cleaved from the benzene ring. If this reaction occurs, *m*-xylene would be a metabolite. No 4'-hydroxybupivacaine was detected in the urine of rats in contrast to humans. The amount of metabolites as a percentage of the recoverd metabolites in the entire sample was provided. The relative amounts of PPX, bupivacaine, and the 2-monohydroxylated isomers combined were the same. The amount of 3-hydroxybupivacaine was 2/3 that of the other three forementioned metabolites. All of the 3'-hydroxybupivacaine and the 4-hydroxylated BUPOH metabolite were conjugated. The two monohydroxylated metabolites [BUPOH] are actually two distinct compounds but are catalogued by CAS as one compound with unspecified atachment of the hydroxyl group (either 4 or 5).	Dennhardt et al. (1978a) and Dennhardt (1981)
24 Female Sprague-Dawley Rats	Single s.c. dose with 2 mg/kg of [pipecolyl-G-^{3}H]-bupivacaine	Determined distribution, biotransformation, and excretion of bupivacaine in the rat. Compounds found were: Bupivacaine [BUP] (2.8% of the total dose) 3'-Hydroxybupivacaine [3'-BUPOH] (24.0%) * 2,6-xylidine was not mentioned as a metabolite but is likely since PIP was reported	Radioactivity was found in all tissues examined, and in most tissues the maximum concentration of radioactivity was found within the first 15 min after s.c. administration. The tissue concentrations ranged from 7.4 nmol bupivacaine/g tissue in the adrenal glands to less than 1 nmol bupivacaine/g tissue in the blood, eye, and muscle. After the adrenal glands, the tissues with the highest concentrations of radioactivity were, from most to least concentrated, the lung, kidney, liver, fat, spleen, and heart. The injection site still contained 50% of the dose 30 min after injection, which decreased to 30% after 1 hr, and 19% after 2 hr. The amount of radioactivity found in the intestinal contents peaked at 42% of the dose after 6 hr, with 4% remaining after 24 hr, indicating biliary excretion of bupivacaine with reabsorption in the intestine. After 24 hr, 50% of the dose had been recovered in the urine and 28% in the feces. No desbutylbupivacaine [PPX], 4'-hydroxydesbutylbupivacaine [4'-PPXOH], or 4'-hydroxybupivacaine [4'-BUPOH] were found in the urine of the rats. Only 2.2% of the 3'-hydroxybupivacaine was found as free and unconjugated in the urine. Hydroxylation in the 3'-position is the principal metabolic pathway in the rat.	Goehl et al. (1973)

Table A-1. Metabolism Studies of Bupivacaine in Humans and Experimental Animals (Continued)

Subjects	Dose	Compounds Measured[a]	Remarks	Reference
3 Female Wistar Albino Rats	i.p. injection of carbonyl ^{14}C-labeled bupivacaine (30 mg/kg; 2.5 µCi/rat) (labeled in the carbonyl group of the pipecolyl moiety)	Bupivacaine [BUP] (3.4% of urinary ^{14}C found in 1st 24-hour urine collection) Desbutylbupivacaine [PPX] (1.1%); 3'-Hydroxybupivacaine [3'-BUPOH] (45.3%) 4'-Hydroxybupivacaine [4'-BUPOH] (28.3%) Pipecolic acid [PIP] (6.0%) Unknown 1 (neutral) (2.2%) Unknown 2 (acidic) (13.1%)	Urine and feces were collected for 4 days and excretion of radiolabeled bupivacaine was determined. Twenty-nine percent of the bupivacaine dose was found in the feces and 27% in the urine in the first 24-hr collection. The total percentage of the bupivacaine dose recovered in 4 days was 74% (urine 33%, feces 41%). The major routes of metabolism in the rat were hydroxylation of the aromatic ring of the bupivacaine molecule to give 3'-hydroxy- and 4'-hydroxybupivacaine. The minor pathway involved N-dealkylation to give desbutylbupivacaine (PPX) and then hydrolysis of the amide bond to give pipecolic acid and one might presume 2,6-xylidine plus metabolites totaling the same fraction (6%). This metabolism was similar to that of mepivacaine and lidocaine; however, N-dealkylation of the ring was much lower in bupivacaine when compared to that of lidocaine. This may be due to the size of the *N*-*n*-butyl group in bupivacaine and steric hindrance associated with the pipecolic acid moiety.	Caldwell et al. (1977 abstr.)
4 Female Wistar Albino Rats	i.p. injection of ^{14}C-labeled bupivacaine (30 mg/kg; 2.5 µL/rat) (labeled in the carbonyl group of the pipecolyl moiety)	Bupivacaine [BUP] (0.9% of dose found in 1st 24-hour urine collection) Desbutylbupivacaine [PPX] (0.3%); 3'-Hydroxybupivacaine [3'-BUPOH] (12.1%) 4'-Hydroxybupivacaine [4'-BUPOH] (7.7%) Pipecolic acid [PIP] (1.6%) Unknown (0.6% neutral and and 3.5% acidic)	Urinary and fecal excretion values reported were the same as those reported by Caldwell et al. (1977 abstr.). The reason for the lower amount of metabolites reported was not immediately evident. A paper by Caldwell et al. in preparation in 1977 was cited as the source for the data. 3'-Hydroxy- and 4'-hydroxybupivacaine were detected primarily (~80%) as glucuronide conjugates.	Caldwell et al. (1978)

Table A-1. Metabolism Studies of Bupivacaine in Humans and Experimental Animals (Continued)

Subjects	Dose	Compounds Measured[a]	Remarks	Reference
2 Female Sprague-Dawley Rats	i.m. injection of 15 mg/kg bwbupivacaine hydrochloride	Bupivacaine [BUP] (0.76% of the dose recovered in a 12-hr urine collection) Desbutylbupivacaine [PPX] (0.02%) 3'-Hydroxybupivacaine [3'-BUPOH] (0.18%) 4'-Hydroxybupivacaine [3'-BUPOH] (0.04%)	Urine was collected for 12 hours after i.m. administration and the total dose recovered in the urine was about 1%. This study was mainly to evaluate HPLC methods for the determination of metabolites of bupivacaine and lidocaine. A run buffer pH of 5.0 permitted baseline resolution of all compounds in 15 min.; however, at pH 6.0 and 7.0, although run time was reduced, there was co-migration of the 3'- and 4'-hydroxybupivacaine isomers. Injection time was also an important factor in obtaining accurate results. An injection time of 45 sec permitted good resolution of all compounds.	Schieferecke et al. (1998)
36 Sheep (Strain and Sex n.p.)	Dosed i.v. with bupivacaine (6.28 □mol/kg bw) and	Urine was analyzed 30 min after administration. The compounds detected and their amounts were: 3'-Hydroxybupivacaine [3'-BUPOH] (39 □M) 4'-Hydroxybupivacaine [4'-BUPOH] (3 □M) Pipecoloxylidide [PPX] (1.4 □M) 3'-Hydroxypipecoloxylidide [3'-PPXOH] (6 □M) 4'-Hydroxypipecoloxylidide [4'-PPXOH] (<3 □M) Bupivacaine [BUP] (<1.0 □M)		Arvidsson et al. (1999)

[a] Names are given as written in the original article.
Because of the variation in nomenclature used, each compound name is followed by a code, which is used in any list of metabolites and metabolic pathways.

Abbreviations: bw = body weight; hr = hour(s); i.p. = intraperitoneal; i.v. = intravenous; i.m. = intramuscular; min = minute(s); n.p. = not provided; s.c. = subcutaneous; sec = second(s); yr = year(s)

Table A-2. Pharmacokinetics Studies of Bupivacaine in Humans and Experimental Animals

Subjects	Dose	Remarks	Reference
In Vivo Studies			
8 Healthy Human Males (20-42 yrs)	Continuous 21-hr epidural infusion with 0.25% bupivacaine (2.5 mg/mL) at a rate of 10 mL/hr (25 mg/hr)	The plasma concentrations of bupivacaine increased continuously (linearly) throughout the 21-hr infusion period, reaching a plateau (designated as $C_{5\text{-}10}$) at approximately 5 to 10 hr after the start of infusion $C_{5\text{-}10}$. The mean $C_{5\text{-}10}$ plateau level was 0.7 mg/L. The mean peak plasma level was 0.90 mg/L, observed at the termination of infusion at 21 hr. The mean half-life in plasma, measured after infusion termination, was 5.1 hr. The rate of clearance was 423 mL/min. These values were all for total plasma concentration, including protein-bound fractions (95.2%).	Emanuelsson et al. (1995)
18 Pregnant Women and Their Fetuses	Lumbar epidural anesthesia established with a dose of 35 mg bupivacaine; later amounts were adminstered at the patients' request (doses n.p.)	Maternal and fetal plasma concentrations were measured prior to and at delivery. Bupivacaine concentrations peaked (~200 ng/mL) in the mother 10 min after injection and decreased monoexponentially with a mean half-life of 1.05 hr (1.25 hr in adult volunteers). Bupivacaine was detected in fetal blood (whole blood or plasma not stated) (29 ng/mL) 10 min after injection in the mother, indicating very rapid placental transfer. The fetal blood level rose to 44 ng/mL at 75 min and remained at that level until the end of sampling at 90 min. Concentrations of bupivacaine in maternal vein and umbilical vein were 263 µg/mL (range 91-430) and 95 µg/mL (range 29-274), respectively. The mean umbilical vein/umbilical artery plasma ratio was 1.19, ranging from 0.68 to 1.67. The mean fetal/maternal venous concentration ratio was 0.33. Bupivacaine decreased monoexponentially in one neonate from about 70 ng/mL at delivery to <10 ng/mL 48 hr following delivery, with a terminal-phase elimination half-life of 21 hr. The mean neonatal elimination half-life in blood was 15.7 hr. Neonatal elimination was biphasic with a rapid elimination phase in the first 2 hr after delivery followed by a slower phase. The initial rapid phase could be due to first-pass elimination in the newly matured lungs. Neither 3'- nor 4'-hydroxybupivacaine was found in the blood of neonates whose mothers received bupivacaine during delivery.	Caldwell et al. (1978)
1 Pediatric Patient (Age and Sex n.p.)	Epidurally administered bupivacaine (1 mg/kg) plus ketamine (0.5 mg/kg bw)	Samples were analyzed for bupivacaine and ketamine concentrations in 76 pediatric patients undergoing surgery; however, only one patient's results were provided in the report. Gantenbein et al. (1997) have shown that administration of ketamine plus bupivacaine resulted in the inhibition of bupivacaine metabolism and prolongation of its half-life. Plasma concentrations of bupivacaine measured at 10, 20, and 45 min after bupivacaine administration were around 420, 560, and 470 ng/mL, respectively.	Gross et al. (1999)

Table A-2. Pharmacokinetics Studies of Bupivacaine in Humans and Experimental Animals (Continued)

Subjects	Dose	Remarks	Reference
19 Mothers and Their Fetuses/Neonates	Epidural administration of 0.25% bupivacaine (Total doses ranged from 25 to185 mg over a maximum of 7.5 hr.)	Maternal plasma concentrations of bupivacaine ranged from 0.1 to almost 0.3 µg/mL, with the highest concentration in a mother that received 25 mg 48 min before delivery. The mean cord-maternal ratio was 0.59. Plasma concentrations of bupivacaine in the mother and the fetus may peak around 45 min before delivery. Eleven babies had eliminated all bupivacaine 24 hr after delivery and 8 had plasma concentrations between 0.005 and 0.01 µg/mL. The two babies that did have higher concentrations of bupivacaine (concentration n.p.) in plasma were the ones whose mothers received large doses, mainly 60 mg in 2 hr and 130 mg in 5.5 hr. Much more bupivacaine crosses the placenta than formerly thought.	Cooper et al. (1977)
3 Pregnant Women and Their Fetuses	Epidural injection of bupivacaine (52 to 135 mg, duration not specified)	Maternal venous and fetal scalp blood were analyzed. The mean maternal bupivacaine concentrations were 173 ± 27.8 ng/mL at 20 min after dosing and 100 ± 14.2 ng/mL at 60 min. Fetal bupivacaine concentrations were 29 ± 5.6 ng/mL at 20 min and 34 ± 8.5 ng/mL at 60 min following administration. The α-phase elimination half-life in mothers was reported as 5 min. The β-phase elimination half-life was much longer in the infants (25 hr) than in the mothers (1.25 hr). Maternal bupivacaine concentrations in blood at the time of delivery were 225 ± 32.1 ng/mL. Umbilical vein bupivacaine concentrations were 66 ± 11.5 ng/mL and the fetal blood concentrations of bupivacaine had increased at 2 hr after administration to 41 ± 12.3 ng/mL. Less than 2% of the dose was determined as bupivacaine in the urine of adults, which suggests extensive metabolism. Neonates cannot metabolize bupivacaine to the extent that adults can and therefore higher concentrations of unchanged bupivacaine are found in the neonatal bloodstream.	Caldwell et al. (1976)

Table A-2. Pharmacokinetics Studies of Bupivacaine in Humans and Experimental Animals (Continued)

Subjects	Dose	Remarks	Reference
80 Mothers undergoing Emergency and Elective Cesarean Section.	All patients received 0.5% bupivacaine (20 mL initial extradural dose and further doses were administered when needed). Bupivacaine Dose: Elective 1.6 ± 0.61 mg/kg, Emergency 3.0 ± 0.8 mg/kg bw). Half of patients also received epinephrine (Elective 1.5 ± 0.3 mg/kg, Emergency 2.9 ± 1.1 mg/kg)	Umbilical venous (UV), umbilical artery (UA), and maternal venous (MV) concentrations of bupivacaine were measured at delivery. The mean plasma concentrations of bupivacaine in elective patients without epinephrine were 0.644 ± 0.378 µg/mL in MV, 0.187 ± 0.083 in UV, and 0.138 ± 0.060 in UA. The mean plasma concentrations of bupivacaine in elective patients with epinephrine were 0.513 ± 0.118 µg/mL in MV, 0.168 ± 0.074 in UV, and 0.177 ± 0.060 in UA. The mean plasma concentrations in emergency patients without epinephrine were 0.915 ± 0.273 µg/mL in MV, 0.326 ± 0.145 in UV, and 0.286 ± 0.151 in UA. The mean plasma concentrations in emergency patients with epinephrine were 0.862 ± 0.223 µg/mL in MV, 0.318 ± 0.154 in UV, and 0.287 ± 0.116 in UA. The effect of "first dose to delivery" and "last dose to delivery" on plasma concentrations of bupivacaine were examined. There was a positive correlation between first dose to delivery on UV, UA, and MV plasma concentrations. There were mostly negative correlations between last dose to delivery and UV:MV, but no significant correlation between UA:MV. Peak plasma concentrations of bupivacaine depended on total dose but not dose rate. However, plateau plasma concentrations were found to reflect dose rate. Since the elimination half-life of bupivacaine in humans is about 6 hr, it is unlikely that a plateau level would be achieved during a normal obstetric epidural block. Since pH and protein binding play a role in placental transfer and may create interindividual differences in absorption, the UA:UV ratio can be used to eliminate these differences and determine fetal equilibration. The ratio of UA to UV increased with last dose to delivery but not with first dose to delivery, indicating that equilibration occurred in about 30 min during each dosage interval (in one circulation). Epinephrine lowered MV and UV plasma concentrations of bupivacaine, but raised UA plasma concentrations. Epinephrine was associated with higher fetal to maternal plasma concentrations. In 8 patients who received epinephrine and whose delivery occurred within 4-52 min from the last dose of bupivacaine UA:UV ratios were markedly above 1. In 5 of these patients, relatively low concentrations of bupivacaine in plasma were promoting reverse placental transfer.	Reynolds et al. (1989)

Table A-2. Pharmacokinetics Studies of Bupivacaine in Humans and Experimental Animals (Continued)

Subjects	Dose	Remarks	Reference
40 Nulliparous Pregnant Females	Intrathecal injection with 2.5 mg bupivacaine and 25 µg fentanyl; subsequent epidural boluses of 10-15 mL of a low-dose mixture containing 0.1% bupivacaine and 2 µg/mL fentanyl. Total bupivacaine dose: 15-185 mg	Mean maternal plasma concentration of bupivacaine at delivery was 0.32 µg/mL (range 0.05-0.91), with 0.02 µg/mL (range 0.00-0.07) free. Mean umbilical venous concentration was 0.15 µg/mL (0.03-0.47), with 0.02 (range 0.00-0.07) unbound. The umbilical venous/maternal plasma ratios of total bupivacaine (mean 0.42, range 0.14-0.82) were lower than the total concentration ratio of fentanyl (mean 1.12, range 0.44-1.98). The mean free drug umbilical venous/maternal venous ratios for bupivacaine and fentanyl were 1.12 (range 0.44-1.98) and 1.20 (range 0.06-3.41), respectively. All Apgar scores were >7 within 5 min after delivery. There were no correlations between Apgar scores, umbilical blood gases, or neurobehavioral scores and umbilical venous concentrations of either bupivacaine or fentanyl.	Fernando et al. (1997)
2 Fetuses [40-wk-old Fetus M and 24-wk-old Fetus J] born alive to mothers that had undergone epidural anesthesia	Mother of Fetus M received a total dose of 125 mg bupivacaine (time n.p.); Mother of Fetus J received a total of 87.5 mg bupivacaine	Fetus M (2790 g) was born anencephalic and died of post-partum asphyxia 21 min after birth. Fetus M did breathe immediately and spontaneously for the 21 min. Fetus J was born as a result of induced birth due to the mothers' metastatic intestinal carcinoma. The fetus died 3 min after birth. Nine hours before the birth of Fetus M, the maternal venous/umbilical venous ratio of bupivacaine concentration was nearly 1.0 (Fetus M: 179 ng/mL; maternal: 180 ng/mL). The concentration of bupivacaine in the lungs of Fetus M was 40 times higher than the fetal plasma concentration and concentrations in the heart were 3 times higher than in plasma. Fetus M bupivacaine concentrations in the liver, kidneys, gall bladder, and thymus were around twice the plasma concentrations. Fetus M bupivacaine concentration in fat was low and concentrations in the muscle were slightly above plasma concentrations. Fetus J had the highest bupivacaine concentrations in the liver (2.5 times higher than plasma concentrations). All other organ/plasma ratios were between 1 and 2. The high concentrations in the lungs were attributed to bupivacaine's high rate af perfusion after spontaneous respiration due to the closure of the ductus arteriosus. Also, increasing agonal respiratory acidosis results in the accumulation of bupivacaine in the lung, where the ionized form is unable to leave the cellular space. Under acidotic conditions, there may be an increase of perfusion of local anesthetics into the placental space.	Müller-Holve et al. (1986)

Table A-2. Pharmacokinetics Studies of Bupivacaine in Humans and Experimental Animals (Continued)

Subjects	Dose	Remarks	Reference
20 Male Surgical Patients (ages 20-81 yr)	subarachnoid administration of 13.3 mL bupivacaine hydrochloride (0.5%)	The terminal elimination rate constant decreased with increasing age, whereas the terminal half-life and mean residence time increased with age. Absorption of bupivacaine was rapid in all patients. There was a positive correlation between the time that peak plasma concentrations were detected and age. The mean absorption time in older patients is shorter due to a more rapid late absorption phase that may be due to greater local blood flow or a decrease in local binding; however, this shorter absorption does not effect the duration of action in older patients, possibly due to the drug's pharmacodynamics. No correlation was observed between the maximum concentration detected and age. Eighteen patients exhibited absorption of bupivacaine that fit biexponential equations, whereas the remaining two showed monoexponential absorption.	Veering et al. (1991)
6 Healthy Human Volunteers	i.v. administration of bupivacaine (50 and 25 mg) and etidocaine (50 and 25 mg) on 4 separate occasions in each volunteer	The authors conceeded that the doses were very small and may not reflect actual values achieved at higher doses; however, the relative pharmacokinetics are important. The plasma levels of bupivacaine and etidocaine exhibited a biphasic characteristic, which represents the equilibration of the local anesthetic in a two-compartment open system. The first phase represents a rapid decline in plasma levels due to absorption into the tissues and the second phase represents clearance from the body. At equivalent i.v. doses, bupivacaine produces higher plasma concentrations than etidocaine, which may be due to the partition coefficients and protein binding, creating a greater amount of tissue distribution for etidocaine. In isolated perfused guinea pig liver, the rates of metabolism of lidocaine, bupivacaine, and etidocaine were very similar. If blood flow is considered to be constant in normal healthy individuals, then the overall elimination of the local anesthetics would be inversely related to the volume of distribution.	Scott et al. (1973)
15 Near-term Pregnant New Zealand White Rabbits	i.v. infusion of 12.5 mg bupivacaine and 12.5 mg pethidine over 80 min	The study showed that fetal transfer rates after administration of bupivacaine or pethidine are not affected by concomitent administration of the other drug. Both drugs were cleared more rapidly from maternal plasma than from fetal plasma.	Hamshaw-Thomas and Reynolds (1985)

Table A-2. Pharmacokinetics Studies of Bupivacaine in Humans and Experimental Animals (Continued)

Subjects	Dose	Remarks	Reference
40 Near-term Pregnant Rabbits (Strain n.p.)	i.v. administration of ^{3}H-labeled bupivacaine (0.3 mg/kg bw) in one group and administration of ^{3}H-labeled lidocaine (0.6 mg/kg bw) in another group of rabbits.	There was no significant difference in the bupivacaine- and lidocaine-treated animals with respect to pH (7.52 and 7.53) and oxygen pressure (169 and 153 mm Hg) in plasma, but the arterial carbon dioxide values were slightly higher in the bupivacaine group (28.2 ± 1.12 mm Hg) when compared with the lidocaine-treated group (24.5 ± 1.02 mm Hg). Maternal heart/blood local anesthetic concentration ratios were calculated and it was found that at 2 min, the heart/blood ratio in the lidocaine group (4.1) was 4 times higher than in the bupivacaine-treated group (1.03). At 5 min, it was twice as high (2.1 and 1.2). The fetal/maternal blood ratios of bupivacaine were 0.37 (2 min) and 0.41 (5 min), and fetal/maternal blood ratios of lidocaine were 0.64 (2 min) and 0.82 (5 min). The fetal heart/blood ratios were constant over time in both groups, with the lidocaine group having 1.06 and bupivacaine having only a 0.60 ratio. The fetal brain/blood ratios were constant over time, with the ratio in bupivacaine-dosed rabbits being 0.43 and the lidocaine group exhibiting a ratio of 1.09. The fact that the ratios of fetal brain/blood and fetal heart/blood were constant with time in both groups indicates an early equilibrium between fetal tissue and blood. The fact that the fetal heart/blood and fetal brain/blood ratios were lower in the bupivacaine group suggests an advantage to using bupivacaine rather than lidocaine in obstetric analgesia. The lower fetal/maternal blood concentrations in the bupivacaine-dosed group indicated slower placental transfer or permeability of bupivacaine when compared to lidocaine.	Hollmén (1973)
16 Pregnant New Zealand White Rabbits	i.v. infusion of bupivacaine (1.25 mg/mL) solution, either plain (n = 8) or with epinephrine (1.25 μg/mL) (n = 8). Total infusion was 15 mg bupivacaine and 15 μg epinephrine in 2 hr.	The coadminstration of epinephrine with bupivacaine was associated with higher concentrations of bupivacaine in placental tissue and may be responsible for increases in fetal plasma and brain; however, the use of extradural epinephrine should not significantly increase bupivacaine toxicity. Fetal/maternal plasma concentration ratios increased until a plateau was reached (~ 0.3) and even though fetal brain/plasma ratios were high, the concentration of bupivacaine in the fetal brain was lower than concentrations found in maternal brains, even after 2 hr of administration. There was no evidence to support the theory that low fetal/maternal plasma concentrations are due to extensive tissue uptake in the fetus. The effect was predominently the result of differences in α-acid glycoprotein binding.	Laishley et al. (1989)

Table A-2. Pharmacokinetics Studies of Bupivacaine in Humans and Experimental Animals (Continued)

Subjects	Dose	Remarks	Reference
White Rabbits (Strain, Sex n.p.)	i.v. infusion of ^{3}H-labeled bupivacaine (0.06 mg/kg/min) over 20-40 min	The concentration of bupivacaine found in the blood of acidotic rabbits (n=3) was twice that of concentrations in normal rabbits (n=3) during the 20-min infusion period. The distribution of bupivacaine under normal and acidic conditions is affected by the plasma concentration of bupivacaine, blood flow, and uptake of the drug in different organs. Bupivacaine did not penetrate erythrocytes to any appreciable extent; however, penetration of bupivacaine *in vivo* is increased by acidotic conditions. In rabbits with normal pH, the bupivacaine concentration in the lungs was 8 times higher, and liver and kidney concentrations were 6 times higher than blood plasma concentrations. The concentration of bupivacaine in the lungs decreased rapidly within 20 min after infusion termination. In rabbits with acidosis, higher concentrations of bupivacaine were found in certain organs. For example, the lungs of rabbits with acidic blood contained bupivacaine concentrations 5 times higher than those in the lungs of normal rabbits and 25 times higher than plasma concentrations in acidotic animals. The risk of complications with the use of local anesthetics may increase in the presence of acidosis, which may emanate from the altered ratio of ionized and un-ionized forms of the anesthetic in plasma.	Sjöstrand and Widman (1973)
Rats (Strain and Sex n.p.)	i.v. injection of bupivacaine (Dose n.p.)	The elimination half-life ($t_{1/2}$) was 24.7 min. The k_2 was 1.467 hr and the volume (V) was 1.492 L. The hepatic clearance of bupivacaine in the rat was 12 mL/kg/min. Absorption of bupivacaine from the jejunum was rapid. The enterohepatic circulation can be considered negligible since biliary excretion of bupivacaine was very small.	Dennhardt et al. (1978b)
Rats (Strain and Sex n.p.)	Enteral administration of bupivacaine (Dose n.p.)	The elimination half-life was 0.462 hr (27.7 min).	Dennhardt (1981)
10 Perfused Single Human Placental Cotyledons	500-µg bolus in 10 µL of distilled water [lidocaine (*n* =5)] or 20 µL of distilled water (bupivacaine) added to maternal reservoir; 25 mg of antipyrine in 100 µL of distilled water used as a reference compound.	The transfer of lidocaine across the placenta was compared to bupivacaine. To account for differences in placental characteristics, values were normalized with respective antipyrine data. Maternal disappearance of lidocaine ($t_{1/2}$ = 33.0 ± 9.8 min) was not as rapid as that of bupivacaine ($t_{1/2}$ = 26.3 ± 4.8 min). This half-life was the initial phase of a biphasic semilogarithmic maternal plasma concentration curve. However, more lidocaine (22.1 ± 2.21%) than bupivacaine (14.6 ± 2.99%) was transferred across the placenta after 2 hr. The fetal/maternal plasma concentration ratio after 2 hr was 0.90 ± 0.09 for lidocaine and 0.56 ± 0.12 for bupivacaine. The greater amount of lidocaine detected in the fetal compartment could be a result of the greater lipophilicity and hence greater placental tissue binding of bupivacaine. Although the fetal/maternal concentration ratios were much higher than have been seen *in vivo*, it could be due to fetal tissue absorption or protein binding, both of which were absent in this study.	Ala-Kokko et al. (1995)

Table A-2. Pharmacokinetics Studies of Bupivacaine in Humans and Experimental Animals (Continued)

Subjects	Dose	Remarks	Reference
23 Male Wistar Rats	Lung perfused with ~2.0 µg/mL of bupivacaine; liver perfused with 2, 10, and 100 µg/mL to determine liver clearance rates.	*In situ* lung clearance for prilocaine, bupivacaine, and mepivacaine was measured and compared to liver clearance rates in perfused liver. The closed system pulmonary clearance of bupivacaine was 0.14 ± 0.03 mL/g • min (16 ± 3% of hepatic activity). The isolated perfused rat liver exhibited clearance rates equal to the perfusion rates at low (2 µg/mL), intermediate (10 µg/mL), and high (100 µg/mL) doses (clearance = 1 mL/g • min). Extrahepatic pulmonary elimination of bupivacaine was detected in a closed system but it was not much different from that of prilocaine (20%) or mepivacaine (12%). The lung could function as a short-term buffer for large doses of bupivacaine.	Geng et al. (1995)
6 New Zealand White Rabbits (Sex n.p.)	Lung infused with two 0.5 mL boluses of indocyanine green (1 mg/mL) and bupivacaine (2.5 mg/mL or 0.5 mg/kg), second bolus administerd 5 sec after end of first run; one rabbit received only the first bolus	The post pulmonary recovery rate was calculated as about 63%, with very wide variation from one rabbit to another. The same venous pulmonary concentration of bupivacine was seen on first pass (first bolus) and in the subsequent bolus administrations. This study showed that bupivacaine fractions are held by the lungs in the extravascular space, with later back diffusion into the circulation. As in other studies, it was concluded that pulmonary absorption of bupivacaine has implications for systemic toxicity by delaying the passage of bupivacaine and delaying peak systemic concentrations. Drugs that may diminish the uptake or increase passage of bupivacaine through the lungs may increase the risk of cardiac and cerebral toxicity.	Palazzo et al. (1991)
In Vitro Studies			
Fischer 344 Rat Hepatocytes (from rats older than 30 mo)	Hepatocyte concn. was 10^6/mL; 20-100 µg/mL bupivacaine (69-347 µM) added with and without 100 µg/mL cimetidine (396 µM); incubated for 2 hr	There was an age-related effect on the metabolism of bupivacaine, which was seen as a 37% reduction in the V_{max} in elderly male rat P450s. This reduction was correlated with other studies that showed a 63% reduction in the amount of P450s from aged rats. There did not appear to be any structural or functional changes that interfered with the metabolic activity of the enzymes for bupivacaine. The rate of bupivacaine clearance is reduced in male rats over 30 mo of age.	Thompson et al. (1987)

Abbreviations: bw = body weight; hr = hour(s); i.m = intramuscular; i.v. = intravenous; min = minute(s); mo. = month(s); n.p. = not provided; sec = second(s); yr = year(s)

APPENDIX B

Metabolism and Pharmacokinetics of Etidocaine

APPENDIX B

This appendix contains details of studies on the metabolism and pharmacokinetics of etidocaine. The metabolites and proposed metabolites of etidocaine are listed in the compounds measured column of **Table B-1**. A key to the codes used for the metabolites of etidocaine is given below along with the organization of Appendix B.

Key to Etidocaine Metabolite Codes

Code	Compound	Code	Compound
ETI	2-*N*-Ethylpropylamino-2-butyroxylidide; Etidocaine	IMZ04	2-Methyl-*N*-2,6-dimethylphenyl-5-ethyl-4-imidazolidinone
EtABX	2-*N*-Ethylamino-2'-butyroxylidide	4-XYLOH	4-Hydroxy-2,6-dimethylaniline; 4-Hydroxyxylidine
PrABX	2-*N*-Propylamino-2'-butyroxylidide	3'-EtABXOH	*N*-(2,6-Dimethyl-3-hydroxyphenyl)-2-(*N*-ethylamino)butyramide
ABX	2-Amino-2'-butyroxylidide	4'-EtABXOH	*N*-(2,6-Dimethyl-4-hydroxyphenyl)-2-(*N*-ethylamino)butyramide
IMZ01	3-(2,6-Dimethylphenyl)-5-ethyl-2,4-imidazolidinedione	3'-PrABXOH	*N*-(2,6-Dimethyl-3-hydroxyphenyl)-2-(*N*-propylamino)butyramide
IMZ02	1-(2,6-Dimethylphenyl)-2-methyl-4-ethyl-2-imidazolin-5-one	4'-PrABXOH	*N*-(2,6-Dimethyl-4-hydroxyphenyl)-2-(*N*-propylamino)butyramide
IMZ03	1-(2,6-Dimethylphenyl)-2,4-diethyl-2-imidazolin-5-one	3'-ETIOH	*N*-(2,6-Dimethyl-3-hydroxyphenyl)-2-(*N*,*N*-ethylpropylamino)butyramide
3'-ABXOH	*N*-(2,6-Dimethyl-3-hydroxyphenyl)-2-aminobutyramide	4'-ETIOH	*N*-(2,6-Dimethyl-4-hydroxyphenyl)-2-(*N*,*N*-ethylpropylamino)butyramide
4'-ABXOH	*N*-(2,6-Dimethyl-4-hydroxyphenyl)-2-aminobutyramide	XYL	2,6-Dimethylaniline; 2,6-Xylidine

Table B-1. Metabolism Studies of Etidocaine in Humans

Subjects	Dose	Compounds Detected	Remarks	Reference
In Vivo Studies				
1 Male Volunteer	Oral administration of etidocaine hydrochloride (200 mg)	*N*-(2,6-Dimethyl-3-hydroxyphenyl)-2-aminobutyramide [3'-ABXOH] *N*-(2,6-Dimethyl-4-hydroxyphenyl)-2-aminobutyramide [4'-ABXOH] *N*-(2,6-Dimethyl-3-hydroxyphenyl)-2-(*N*-ethylamino)butyramide [3'-PrABXOH] *N*-(2,6-Dimethyl-4-hydroxyphenyl)-2-(N-ethylamino)butyramide [4'-EtABXOH] *N*-(2,6-Dimethyl-3-hydroxyphenyl)-2-(N-propylamino)butyramide [3'-PrABXOH] *N*-(2,6-Dimethyl-4-hydroxyphenyl)-2-(N-propylamino)butyramide [4'-PrABXOH] *N*-(2,6-Dimethyl-3-hydroxyphenyl)-2-(*N*,*N*-ethylpropylamino) butyramide [3'-ETIOH] *N*-(2,6-Dimethyl-4-hydroxyphenyl)-2-(*N*,*N*-ethylpropylamino) butyramide [4'-ETIOH]	Extraction and analysis of a 48-hr urine collection from a healthy human volunteer resulted in the determination of eight dealkylated and hydroxylated metabolites of etidocaine. Quantitative analysis of the metabolites was not possible because of the methods used; however, it was estimated that these metabolites accounted for approximately 10% of the total dose of etidocaine	Vine et al. (1978)

Table B-1. Metabolism Studies of Etidocaine in Humans (Continued)

Subjects	Dose	Compounds Detected	Remarks	Reference
1 Female and 1 Male Volunteer	Epidural injection of etidocaine in the female (150 mg); Oral dose of etidocaine in the male (200 mg)	2-Amino-2'-butyroxylidide [ABX] 2-*N*-Ethylamino-2'-butyroxylidide [EtABX] 2-*N*-Propylamino-2'-butyroxylidide [PrABX] 2-*N*-Ethylpropylamino-2'-butyroxylidide [ETI] 2-Methyl-N^3-2,6-dimethylphenyl-5-ethyl-4-imidazolidinone [IMZ04] 2,6-Dimethylaniline (2,6-xylidine) [XYL] 4'-Hydroxy-2,6-dimethylaniline [4-XYLOH] Unknown 1 Unknown 2	Examination of 48-hour urine samples from two patients resulted in the isolation of nine metabolites. Two of the nine metabolites were not identified during this study. A quantitative determination of the metabolites was performed on urine collected from the patient receiving the epidural dose. Six metabolites: Unknown #1 (7.3%), Unknown #2 (5.0%), 2-amino-2'-butyroxylidide (9.5%), 2-N-ethylamino-2'-butyroxylidide (0.45%), 2,6-dimethylaniline (0.46%), and 4-hydroxy-2,6-dimethylaniline (8.3%) accounted for approximately 31% of the total dose of etidocaine. 2-Methyl-N^3-2,6-dimethylphenyl-5-ethyl-4-imidazolidinone was only found in the volunteer that had been dosed orally.	Thomas et al. (1976)
Four Patients (sex n.p.)	Epidural administration of etidocaine hydrochloride (dose n.p.)	Xylidine [XYL] *p*-Hydroxyxylidine [4-XYLOH] Other metabolites not specified.	Xylidine and *p*-hydroxyxylidine accounted for only 3.0% of the dose of etidocaine in a 48-hour urine sample compared to 74% of the dose following lidocaine administration. The authors attributed this difference to the presence of the branched alkyl side chain in the etidocaine moiety. Unspecified metabolites accounted for approximately 50% of the dose of etidocaine. Excretion of unconjugated amines accounted for 18% of the dose with acid controlled urine and 3% with alkaline controlled urine.	Morgan et al. (1977a)

Table B-1. Metabolism Studies of Etidocaine in Humans (Continued)

Subjects	Dose	Compounds Detected	Remarks	Reference
2 Male Hernia Patients and 2 Male Volunteers	Epidural administration of etidocaine hydrochloride (140 and 180 mg) for hernia repair; and oral administration of etidocaine hydrochloride (200 mg) in volunteers	Etidocaine [ETI] 1-(2,6-Dimethylphenyl)-2-methyl-4-ethyl-2-imidazolin-5-one [IMZ02] 1-(2.6-Dimethylphenyl)-2,4-diethyl-2-imidazolin-5-one [IMZ03] 3-(2,6-Dimethylphenyl)-5-ethyl-2,4-imidazolidinedione [IMZ01] 2-Amino-2'-butyroxylidide [ABX] 2-*N*-Ethylamino-2'-butyroxylidide [EtABX] 2-*N*-Propylamino-2'-butyroxylidide [PrABX]	The urine samples from the four patients were pooled and the metabolites were determined. The hydantoin metabolite 3-(2,6-Dimethylphenyl)-5-ethyl-2,4-imidazolidinedione [IMZ01] was found to be approximately 10% of the administered dose of etidocaine. Hydantoin compounds have been known to have anticonvulsant properties. This metabolite may be responsible for etidocaine's lower toxicity (when compared to bupivacaine) since one of the symptoms of amide local anesthetic toxicity is convulsions	Morgan et al. (1977c)
6 Patients (4 M and 2 F [nonpregnant]; age: 52-66 yr); 4 Healthy Male Volunteers (age: 22-26 yr), and 14 Healthy Pregnant Women (age: 20-36 yr)	Epidural administration of etidocaine hydrochloride (148 ± 22 mg for nonpregnant patients and 160 ± 36 mg for pregnant patients)	Determined metabolism of etidocaine in pregnant and nonpregnant subjects and placental transfer. Metabolites determined and their amounts in 21- to 47-hr urine collections in pregnant women and nonpregnant subjects and as cord maternal plasma ratio were: Etidocaine [ETI] (0.17%, 0.33% of etidocaine hydrochloride dose; 0.365) 2-Amino-2'-butyroxylidide [ABX] (10.5%, 13.1%; no determination of cord/maternal plasma ratio) 2-Ethylamino-2'-butyroxylidide [EtABX] (1.52%, 2.65; 0.823) 2-Propylamino-2'-butyroxylidide (no urine determination; 0.546) [PrABX] Xylidine [XYL] (2.16%, 0.89%; no determination of cord/maternal plasma ratio) 4-Hydroxyxylidine [4-XYLOH] (0.79, 3.23; no determination of cord/maternal plasma ratio)	The metabolites 2-*N*-ethylamino-2'-butyroxylidide and 2-*N*-propylamino-2'-butyroxylidide were detected in maternal blood within 5 min and cord blood within 30 min of administration. Both the cord/maternal plasma and blood concentration ratios increased in the order of lipid solubility of etidocaine and its metabolites (EtABX>PrABX>ETI).	Morgan et al. (1977b)

Table B-1. Metabolism Studies of Etidocaine in Humans (Continued)

Subjects	Dose	Compounds Detected	Remarks	Reference
Neonates of 11 Full-term Healthy Pregnant Women (age: 20-36 yr old)	Epidural administration of etidocaine hydrochloride (1%) with or without epinephrine; all also received pethidine; 7 mothers received a single dose of etidocaine (mean 155 ± 30 mg; 0.94 ± 0.84 hr pre-delivery)	Determined metabolite concentrations in the urine of mothers and neonates after epidural administration of etidocaine during delivery. Metabolites detected in the urine of mothers and the 21- to 47-hr urine collection from neonates were: 2-Amino-2'-butyroxylidide [ABX] 2-*N*-Ethylamino-2'-butyroxylidide [EtABX] 2-*N*-Propylamino-2'-butyroxylidide [PrABX] *p*-Hydroxyxylidine [4-XYLOH] Xylidine [XYL]	Because the seven mothers received a measurable dose of etidocaine, most calculations were based on their results. The mean percentage of the maternal dose of etidocaine and its three metabolites recovered in neonatal urine was 0.12% (range 0.016-0.28%). Urinary pHs ranged from 5.5-8.5. Estimations of fetal blood concentrations were made using cord blood concentrations and an average neonatal blood volume of 268 mL. The mean total etidocaine in cord blood at birth ranged from 0.100-0.983 µg/mL. The mean total amount of etidocaine in neonatal blood at birth was 96.1 □g (range 26.8-263 □g). The mean percentage of etidocaine in neonatal blood that was excreted in the 48-hr urine collections was estimated to be 14.6 ± 23.3% (range 0.15-70%). The metabolite PrABX was found to be the relatively more abundant metabolite in the urine of the neonates than in the adults. This pattern of N-dealkylation in the neonate is also true for MEGX and PPX as metabolites of lidocaine and mepivacaine, respectively (Mihaly et al., 1977; Moore et al., 1975). ABX was much less abundant in the neonates than in the adults. The mean ratio of urinary excretion of ABX, EtABX, and PrABX to total etidocaine excreted in the urine of neonates was 3.83, 16.4, and 7.57, respectively. The mean ratio of excretion of ABX, EtABX, and PrABX to total etidocaine excreted in the urine of mothers was 116, 14.5, and 1.55, respectively. p-Hydroxyxylidine was found in 3 of 8 neonatal urine samples (range 2-6 □g, volume n.p.). Xylidine was detected in urine of 5 of 8 neonates (range trace-1.9 □g).	Morgan et al. (1978)

Abbreviations: hr = hour(s); i.v = intravenous; yr = year(s)

Table B-2. Pharmacokinetics Studies of Etidocaine in Humans and Experimental Animals

Subjects	Dose	Remarks	Reference
In Vivo Studies			
6 Patients (4 M and 2 F [nonpregnant]; age: 52-66 yr); 4 Healthy Male Volunteers (age: 22-26 yr), and 14 Healthy Pregnant Women (age: 20-36 yr)	Epidural administration of etidocaine hydrochloride (148 ± 22 mg for non-pregnant patients and 160 ± 36 mg for pregnant patients)	The $t_{1/2}$ in pregnant and nonpregnant subjects were not significantly different; however, the variation in clearance in pregnant women was significantly greater than that of the nonpregnant subjects. The mean $t_{1/2}$ was 5.10 ± 2.58 hours in pregnant women (n=7) and was 5.46 ± 1.04 hours in non-pregnant women. Although total systemic blood clearance of etidocaine was not much different in pregnant (14.0 ± 3.5 mL/min/kg) and non-pregnant (14.6 ± 4.6 mL/min/kg) individuals, the plasma clearance was significantly different (12.9 ± 4.4 and 8.60 ± 3.01, respectively). This was assumed to be a result of the lower hematocrit in pregnant women and that almost all of the etidocaine was confined to the plasma in both groups. The concentration of metabolites detected in the 24-hour urine collection from the two groups was not significantly different. The mean protein-bound fraction of etidocaine in the blood was much lower in pregnant women during delivery (73.6%) than in male and female controls (93.4 to 94.8%) or pregnant women at the 35th to 37th week of gestation (94.4%). This finding could be serious since it is the unbound fraction of the local anesthetic that is transferred across the placenta. Placental transfer of etidocaine was rapid (<5 min).	Morgan et al. (1977b)
7 Nonpregnant Adult Ewes and Newborn Lambs, and 6 Fetuses.	i.v. dose with 0.5% etidocaine hydrochloride (2.5 mg/kg bw) into femoral vein over a period of 60 sec in all groups	The peak arterial blood concentration of etidocaine, 1 min after injection, was 5.28 ± 0.8 □g/mL in adult sheep, 1.62 ± 0.18 □g/mL in the neonate, and 0.56 ± 0.15 □g/mL in the fetus. The $t_{1/2\alpha}$ and $t_{1/2\beta}$ were very similar in the adult sheep (5.0 and 34.9 min, respectively) and in the neonate (4.7 and 36.9 min, respectively), but the volume of distribution (V_D) was 3 times greater in the neonate (4.64 L/kg) than in the adult sheep (1.52 L/kg). Total body clearance of etidocaine was more rapid in the neonate (87.4 mL/min/kg) than in the adult (30 mL/min/kg). The greater volume of distribution of etidocaine in the neonate was explained by the fact that highly perfused organs make up a larger percentage of a neonate's body mass. The rapid disappearance of etidocaine (none found after 30 min) from fetal blood was due to placental transfer to the mother as was evident by the appearance of etidocaine (0.29 ± 0.11 □g/mL) in the arterial blood of the mother 1 min after injection into the fetus. The renal clearance of etidocaine in the neonate (2.40 ± 1.22 □g/mL) was much higher than in the adult (0.22 ± 0.8 □g/mL).	Pedersen et al. (1982)

Abbreviations: bw = body weight; F = female(s); i.v. = intravenous; M = male(s); min = minute(s); sec = second(s); $t_{1/2}$ = half-life; $t_{1/2\alpha}$ = initial rapid phase of elimination; $t_{1/2\beta}$ = terminal slow phase of elimination; yr = year(s)

APPENDIX C

Metabolism and Pharmacokinetics of Lidocaine

APPENDIX C

This appendix gives details from studies of the metabolism and pharmacokinetics of lidocaine. The metabolites and proposed metabolites of lidocaine are listed in the compounds measured column of **Table C-1**. A key to the codes used for the metabolites of lidocaine is given below along with the organization of Appendix A.

Key to Lidocaine Metabolites Codes

Codes	Chemical Name	Codes	Chemical Name
LID	Lidocaine	*N*-XYLOH	*N*-Hydroxyxylidine; 2,6-Dimethylphenylhydroxylamine
MEGX	Monoethylglycinexylidide	LID-*N*-Ox	Lidocaine *N*-oxide
GX	Glycinexylidide	EG	*N*-Ethylglycine
3'-LIDOH	3-Hydroxylidocaine	DEG	*N,N*-Diethylglycine
4'-LIDOH	4-Hydroxylidocaine	IMZ05	N^1-Ethyl-2-methyl-N^3-(2,6-dimethylphenyl)-4-imidazolidinone
3'-MEGXOH	3-Hydroxymonoethylglycinexylidide	$C_6H_3Me_2NO$	2,6-Dimethylnitrosobenzene
4'-MEGXOH	4-Hydroxymonoethylglycinexylidide	$C_6H_3Me_2NO_2$	2,6-Dimethylnitrobenzene
3'-GXOH	3-Hydroxyglycinexylidide	XYL	2,6-Xylidine
4'-GXOH	4-Hydroxyglycinexylidide	3-XYLOH	3-Hydroxyxylidine
□-LIDOH	Hydroxymethyllidocaine	4-XYLOH	4-Hydroxy-2,6-xylidine
AMBA	2-Amino-3-methylbenzoic Acid		

Table C-1. Metabolism Studies of Lidocaine in Humans and Experimental Animals

Subjects	Dose	Compounds Detected	Remarks	Reference
In Vivo Studies				
20 Healthy Male Volunteers	Oral administration of lidocaine $HCl \cdot H_2O$ (250 mg, ~ 3.125 mg/kg bw) in gel capsules	Lidocaine [LID] (2.8% of total lidocaine dose) Monoethylglycinexylidide [MEGX] (3.7%) Glycinexylidide [GX] (2.3%) 3-Hydroxylidocaine [3'-LIDOH] (1.1%) 3-Hydroxymonoethylglycinexylidide [3'-MEGXOH] (0.3%) 2,6-Xylidine [XYL] (1.0%) 4-Hydroxy-2,6-xylidine [4-XYLOH] (72.6%)	Urine was collected over a 24-hour period and metabolite concentrations were compared to those of other species. Eighty-four percent of the dose was recovered in 24-hr urine samples. Analysis showed a very high amount of the metabolic product 4-hydroxy-2,6-xylidine. This was more than twice as high as the next highest concentration in the dog (35.2% of the total lidocaine dose). The primary route of metabolism in man was by hydrolysis of the amide bond in lidocaine or one of its dealkylated metabolites. MEGX may be responsible for the emetic effect after lidocaine dosing and has antiarrhythmic activity comparable to lidocaine. Labeling of lidocaine in this study included tritium labeling of the xylidine ring and ^{14}C-labeling of the carbonyl carbon.	Keenaghan and Boyes (1972)
3 Healthy Human Volunteers, Sex n.p.	Oral administration of lidocaine $HCl \cdot H_2O$ (300 mg, ~ 3.125 mg/kg bw) every 8 hr for 7 doses	Monoethylglycinexylidide [MEGX] Lidocaine [GX]	Peak lidocaine concentrations were detected in blood samples from 20 to 60 min after dosing. Total clearance of lidocaine was 15.3, 15.0, and 15.4 mL/min/kg. The mean volumes of distribution of lidocaine at steady state were 1.9, 1.3 and 3.6 L/kg. Half-life of the terminal phase of elimination was 84, 89, and 149 min. Blood MEGX concentrations were comparable to those of lidocaine due to lidocaine's low oral availability and high renal clearance. In contrast, MEGX concentrations are much lower than lidocaine concentrations when lidocaine is administered i.v.. One subject had steady-state concentrations of lidocaine 42% above those predicted. This study revealed that the first-pass effect was not saturable and that individual variations in lidocaine kinetics may change with repetitive administration.	Bending et al. (1976 abstr.)

Table C-1. Metabolism Studies of Lidocaine in Humans and Experimental Animals (Continued)

Subjects	Dose	Compounds Detected	Remarks	Reference
21 Cirrhotic Patients, 9 Acute Hepatitis Patients; 9 Controls, sexes n.p.	Oral administration of lidocaine (5 mg/kg bw) in gel capsules	Monoethylglycinexylidide [MEGX]	Lidocaine serum concentrations (120, 180, and 240 min) and monoethylglycinexylidide (MEGX) serum concentrations (180 and 240 min) were significantly higher in the cirrhotic and hepatitis patients. The half-life for absorption of lidocaine was higher in cirrhosis and hepatitis patients (58 ± 51 and 62 ± 42 min, respectively) when compared to controls (18 ± 19 min). Peak lidocaine serum concentrations were also higher in cirrhosis and hepatitis patients (1.99 ± 0.33 and 0.91 ± 0.31 µg/mL, respectively) than in controls (0.86 ± 0.49 µg/mL). Peak serum MEGX values were higher in hepatitis patients and controls (681 ± 85 and 545 ± 126 µg/mL, respectively) than in cirrhotic patients (387 ± 174 ng/mL).	Muñoz et al. (1999)
41 Cirrhotic Patients (10 M, 22 F)	Single i.v. bolus of lidocaine hydrochloride (1 mg/kg bw) for 2-4 min	Monoethylglycinexylidide [MEGX]	Patients receiving sclerotherapy had MEGX concentrations of < 6 µmol/L to 62 µmol/L 30 min following administration. Patients receiving transjugular intrahepatic portosystemic shunt had MEGX concentrations of 6 to 62 µmol/L 30 min following administration. Patients receiving lidocaine during surgery had MEGX concentrations between 2 and 86 µmol/L 30 min following administration. A patient in the surgical group that did not have liver cirrhosis had a MEGX level of 58 µmol/L.	Schinella et al. (1993)
33 Cardiac Patients, sexes n.p.	Received lidocaine (dose and rate n.p.) for more than one day for treatment of arrhythmia	Monoethylglycinexylidide [MEGX] Glycinexylidide [GX]	Plasma MEGX/lidocaine and GX/lidocaine ratios were 0.36 ± 0.26 and 0.11 ± 0.11, respectively. After serum concentrations were readjusted for protein binding, it was determined that the plasma MEGX/lidocaine ratio was 0.68 ± 0.49. GX was very low (ratio not provided). Steady-state GX serum concentration, normalized to the rate of infusion of lidocaine, decreased with age. It was determined that MEGX plays a greater role in the pharmacokinetics of lidocaine than GX.	Drayer et al. (1983)

Table C-1. Metabolism Studies of Lidocaine in Humans and Experimental Animals (Continued)

Subjects	Dose	Compounds Detected	Remarks	Reference
1 Anhepatic Female Patient awaiting liver transplantation	i.v. administration of lignocaine (1 mg/kg bw) over a 2-min period	Monoethylglycinexylidide [MEGX]	Serum plasma concentrations peaked at 0.89 µg/mL and then underwent an exponential decay over 3 hr (decay of similar concentration was 2 hr in a healthy patient). Serum MEGX concentrations were <10 µg/L at 0 min, 15 µg/L at 15 min, and 30 µg/L at 2 hr, decreasing rapidly after 2 hr. The serum concentration of MEGX in this patient at 15 min was about 20% that of normal subjects, but similar to patients with severe chronic liver disease.	Sallie et al. (1992)
Human Liver Graft Recipients and ESLD (End-stage liver disease) Patients, numbers n.p.	Lidocaine; dose and duration n.p.	Monoethylglycinexylidide [MEGX]	This review of studies that used the lidocaine metabolite MEGX as an indicator of liver function found that MEGX plasma concentrations of <15-25 µg/L 15-30 min after i.v. lidocaine administration indicated severe impairment of liver function.	Potter and Oellerich (1996; cited by Schütz et al., 1998)
One Patient with Normal Liver Function and One with Cirrhosis	i.v. bolus administration of lidocaine hydrochloride (1 mg/kg bw); duration n.p.	Monoethylglycinexylidide [MEGX]	Blood plasma samples from both patients were analyzed before, 15 min after, and 24 hr after dosing. In the normal patient MEGX concentrations were 38 ng/mL 15 min after dosing and 2.5 ng/mL 24 hr after dosing. The cirrhotic patient exhibited plasma MEGX concentrations of 6 ng/mL and 33 ng/mL, respectively.	Laroche et al. (1998)

Table C-1. Metabolism Studies of Lidocaine in Humans and Experimental Animals (Continued)

Subjects	Dose	Compounds Detected	Remarks	Reference
39 Patients with varying liver function	i.v. administration of lidocaine (1 mg/kg bw) over 1 min	Monoethylglycinexylidide [MEGX]	This study was conducted to determine the reliability of different methods for the determination of liver function. Patients were divided into groups according to the extent of liver function determined by other accepted physiological indicators such as bilirubin and cholesterol concentrations, and history of ascites. The mean serum MEGX concentrations, measured 15 min after i.v. injection, were 97 ± 12 □g/L in healthy controls, 42 ± 6 µg/L in patients with high liver function, 26 ± 1 µg/L in patients with moderate liver function, 11 ± 4 □g/L in patients with severe liver function impairment. It was also found that concentrations of MEGX in saliva of lidocaine-dosed patients closely correlated with serum concentrations of MEGX, and that salivary concentration of MEGX was decreased in patients with liver impairment. The determination of MEGX concentrations was a more sensitive indicator of liver function than the prognostic score obtained by other diagnostic means.	Balistreri et al. (1992)
3 Human Males	Oral administration of lidocaine hydrochloride (100 mg); duration n.p.	3-Hydroxylidocaine [3'-LIDOH] 4-Hydroxylidocaine [4'-LIDOH]	The 24-hr urine showed trace amounts of the lidocaine metabolites 3-hydroxylidocaine and 4-hydroxylidocaine (each 0.01-0.02% of dose) after acid hydrolysis. These metabolites were not glucuronide conjugates but may be sulfate conjugated. In other cited studies (McMahon and Woods, 1951; Sung and Truant, 1954), administration of lidocaine led to an increase of urinary sulfate concentrations in man.	Thomas and Meffin (1972)

Table C-1. Metabolism Studies of Lidocaine in Humans and Experimental Animals (Continued)

Subjects	Dose	Compounds Detected	Remarks	Reference
25 Pregnant Women (6 cesarean births, 19 vaginal births)	Pregnant women received epidural administration of lidocaine without epinephrine (mean dose: vaginal birth = 300 ± 193 mg; cesarean = 595 ± 127 mg)	Determined lidocaine, MEGX, and GX concentrations in the plasma and urine of mothers receiving epidural lidocaine for cesarean and vaginal deliveries. Also determined urinary excretion of lidocaine and its metabolites in neonates. Compounds detected in the urine of neonates and mothers were: Lidocaine [LID] Monoethylglycinexylidide [MEGX] Glycinexylidide [GX]	The mothers undergoing cesarean section received a higher dose of lidocaine than mothers undergoing vaginal delivery (dose n.p.). The fetal/maternal plasma concentration ratios of lidocaine, MEGX, and GX after cesarean delivery were 0.66, 1.45, and 1.03, respectively. The fetal/maternal plasma concentration ratios of lidocaine, MEGX, and GX after vaginal delivery were 0.56, 1.18, and 0.80, respectively. MEGX was detected 10 min after the first lidocaine dose and GX was first detected 40 min after the first lidocaine dose in maternal plasma. Both MEGX and GX maternal plasma concentrations increased during delivery and were not statistically different between the cesarean group and the vaginal delivery group. Lidocaine plasma concentrations were higher in the mother, as seen by the plasma concentration ratios; however, the concentration of MEGX was higher in cord blood than in maternal blood. GX concentrations were about the same in both maternal and cord blood. GX was seen in four cord venous blood samples when no GX was detected in the mother. Concentrations of both MEGX and GX (~2 □g drug/mg creatinine) were detected in neonatal urine up to three days after delivery. The urinary excretion of lidocaine in neonates was similar to that of the mother; however, urinary excretion of MEGX and GX was about twice as much in the neonate as in the mother on the first day following delivery and four to five times higher in neonates on the second and third day following delivery.	Kuhnert et al. (1979)

Table C-1. Metabolism Studies of Lidocaine in Humans and Experimental Animals (Continued)

Subjects	Dose	Compounds Detected	Remarks	Reference
2 Patients (with suspected myocardial infarction; Sex n.p.	i.v. dose of lidocaine (2 loading doses of 100 mg lidocaine hydrochloride, 30 min apart), infusion (3 mg/min) began immediately after the first loading dose for up to 48 hr	Measured compounds in urine after collection for 72 hr post-infusion in one patient: Lidocaine [LID] (2.1% of the lidocaine dose) Monoethylglycinexylidide [MEGX] (1.7%) Glycinexylidide [GX] (0.55%) 4-Hydroxylidocaine [4'-LIDOH] (0.28%) 4-Hydroxymonoethylglycinexylidide [4'-MEGXOH] (0.06%) 4-Hydroxyglycinexylidide [4'-GXOH] (0.24%) 4-Hydroxyxylidine [4-XYLOH] (80.1%) 3-Hydroxylidocaine [3'-LIDOH] (0.13%) 3-Hydroxymonoethylglycinexylidide [3'-MEGXOH] (0.04%)	Urine samples were analyzed from one patient while plasma samples were analyzed from another patient. Patients receiving lidocaine as an antiarrhythmic agent for myocardial infarction were studied; however, only the HPLC results from one patient were provided. Plasma and urinary concentrations of lidocaine and its metabolites were determined by HPLC. 4-Hydroxyxylidine was the major metabolite detected in the urine as well as in plasma (4.5 □g/mL immediately after infusion and ~1.7 □g/mL 10 hr post-infusion). The concentration of 4-hydroxyxylidine in plasma was even higher than lidocaine itself (~2.8 □g/mL immediately after infusion and 1.0 □g/mL 10 hr post-infusion). Concentrations of MEGX and GX immediately following infusion were about 0.56 and 0.24 □g/mL, respectively. The concentrations of MEGX and GX 10 hours post-infusion were the same, 0.26 □g/mL. The 3- and 4-hydroxylated metabolites of lidocaine were not detected in plasma (limit of detection = 0.1 □g/mL). Xylidine was not detected at all in this patient and was either "very low" or undetectable in their patient population. 3-Hydroxylidocaine was not detected in the urine of all patients. It is thought that lidocaine may be hydroxylated prior to amide hydrolysis, resulting in formation of little xylidine but large amounts of 4-hydroxyxylidine.	Tam et al. (1987)

Table C-1. Metabolism Studies of Lidocaine in Humans and Experimental Animals (Continued)

Subjects	Dose	Compounds Detected	Remarks	Reference
10 Healthy Male Volunteers	i.v. administration of lidocaine (50 mg) on days 1 to 7 (pretreatment), and days 8 to 14 (with rifampicin treatment, 600 mg total on days 7-12)	Measured the rate of lidocaine metabolism and MEGX formation after induction of the cytochrome P450 isoenzyme CYP3A4 by rifampicin.	Since the deethylation of lidocaine to MEGX is mainly catalyzed by CYP3A4, induction led to higher rates of metabolism of lidocaine and an increase in the formation of MEGX. Lidocaine plasma clearance increased from 7.5 ± 1.2 mL/min/kg, before rifampicin treatment to 8.6 ± 2.0 mL/min/kg following rifampicin treatment. The MEGX concentration in plasma 30 min after dosing was higher with rifampicin treatment (82 ± 34 compared to 61 ± 14 □g/L); however, the maximum concentration of MEGX was not significantly different with (52 ± 10 □g/L) or without (46 ± 9 □g/L) rifampicin. The time to maximum MEGX concentrations in the plasma following administration was shorter during rifampicin treatment (21 ± 11 min) than without (31 ± 16 min). The urinary excretion of 6□-hydroxycortisol indicated that maximum induction of CYP3A4 had occurred. The authors concluded that the formation of MEGX following lidocaine administration could not be used as a sensitive indicator of CYP3A4-dependent liver function when compared to other tests such as cyclosporin A, which results in a tenfold increase when liver function is impaired. It should be noted that the doses used in this study were lower than those used in the MEGX liver function test (1 mg/kg).	Reichel et al. (1998)

Table C-1. Metabolism Studies of Lidocaine in Humans and Experimental Animals (Continued)

Subjects	Dose	Compounds Detected	Remarks	Reference
10 Infants and Children (3-mo-old to 4-yr-old)	Epidural injection of 1% lidocaine (5 mg/kg bw) without epinephrine followed by continuous infusion with lidocaine (2.5 mg/kg/hr)	Measured plasma concentrations of lidocaine and MEGX after continuous epidural infusion in children.	Samples were taken every 30 min for 5 hr following administration. Lidocaine concentrations in plasma increased linearly from 2.5 □g/mL at the beginning of infusion to <3 □g/mL at 5 hr. MEGX concentrations in plasma increased linearly also from about 0.1 □g/mL at the initiation of infusion to about 2.5 □g/mL 5 hr after infusion began. Since MEGX is as toxic as lidocaine, it is important to consider the combined concentration of the two in plasma.	Miyabe et al. (1998)

Table C-1. Metabolism Studies of Lidocaine in Humans and Experimental Animals (Continued)

Subjects	Dose	Compounds Detected	Remarks	Reference
3 Healthy Human Male Subjects	Oral administration of lidocaine hydrochloride monohydrate (250 mg) in two subjects (A and B) and one subject (C) received a molar equivalent of the lidocaine free base (202 mg)	Metabolites were detected in serial plasma and urine collection from the three subjects. Metabolites detected in subjects given lidocaine hydrochloride monohydrate and their mean concentration as a percent of the administered dose in urine: Lidocaine [LID] (4.76%) Monoethylglycinexylidide [MEGX] (12.68%) Glycinexylidide [GX] (0.78%) *m*- and/or *p*-Hydroxylidocaine [3'-LIDOH and/or 4'-MEGXOH] (0.70%) *m*- and/or *p*-Hydroxymonoethylglycinexylidide [3'-MEGXOH and/or 4'-MEGXOH] (0.81%) 2,6-Xylidine [XYL] (0.84%) 4-Hydroxy-2,6-xylidine [4-XYLOH] (65.98%) *N*-Ethylglycine [EG] *N,N*-Diethylglycine [DEG] (>35% of dose) N^1-Ethyl-2-methyl-N^3-(2,6-dimethylphenyl)-4-imidazolidinone [IMZ05] (not detected in urine]	The percentage of the administered dose recovered in the 24-hour urine ranged from 64.2% to 75.2% after treatment of the sample with glucuronidase and sulfatase. The characterization of the non-hydroxylated bases, glycinexylidide and xylidine, was severely reduced after treatment with glucuronidase and sulfatase; however, the detectable amounts of the hydroxylated metabolites was drastically increased. For example, the amount of 4-hydroxyxylidine detected in one patient was 1.37% of the dose before enzyme treatment and 68.2% after enzyme treatment. Between 60.5% and 68.2% of the administered dose was recovered as 4-hydroxyxylidine. All metabolite concentrations were consistently lower after enzyme hydrolysis in Subject C treated with the lidocaine free base, with the exception of *m*- and/or *p*-hydroxylidocaine, which were higher in the individual administered the free base. N^1-Ethyl-2-methyl-N^3-(2',6-dimethylphenyl)-4-imidazolidinone was only quantitated in plasma. The mean plasma concentration peaked at 0.08 μg/mL in Subjects A and B but was not detectable in Subject C 30 min after administration. The mean concentration of N^1-ethyl-2-methyl-N^3-(2',6-dimethylphenyl)-4-imidazolidinone was 0.035 μg/mL at 180 min after administration. *N*-Ethylglycine and *N,N*-diethylglycine were detected, but were not quantitated.	Nelson et al. (1977)

Table C-1. Metabolism Studies of Lidocaine in Humans and Experimental Animals (Continued)

Subjects	Dose	Compounds Detected	Remarks	Reference
3 Human Subjects (Sex n.p.)	Oral dose of lidocaine hydrochloride in two subjects and oral dose of lidocaine hydrochloride with ammonia to decrease urinary pH (5.0-5.3); doses and duration n.p.	Determined the*N*-hydroxyamine metabolite of lidocaine in human urine (time after dose n.p.) and the *in vitro* mutagenic potential of several metabolites in *Salmonella* TA1538 tester strain. Compounds detected were: Lidocaine [LID] MEGX 2,6-Dimethylphenylhydroxylamine [*N*-XYLOH] (1% of administered dose)	There was no apparent difference between the amount of detected metabolites in the ammonia-treated subject and the other subjects. The only *N*-hydroxyamine detected in human urine was 2,6-dimethylphenylhydroxylamine, formed in very low quantities by either the hydrolysis of *N*-hydroxyamines or further oxidation of 2,6-xylidine. This metabolite has also been detected in plasma samples of patients on lidocaine therapy (Strong, J.M., and personal communication). Even if the hydroxyamides had been formed, they would have been considered nontoxic compared to other N-hydroxyamides, such as *N*-hydroxy-2-acetylaminofluorene, which is a potent mutagen and carcinogen. Lidocaine, MEGX, *N*-hydroxylidocaine, *N*-Hydroxymonoethylglycinexylidide, 2,6-xylidine, and 2,6-dimethylphenylhydroxylamine were found to be non-mutagenic, both with and without metabolic activation.	Nelson et al. (1978)
9 Patients Treated for Cardiac Arrhythmias (Number n.p.)	Lidocaine (presumably i.v.) doses ranged from 70 to 3760 mg	Determined 2,6-xylidine-hemoglobin adducts after administration of lidocaine for cardiac arrhythmias. The mechanism of Hb-adduct formation with aromatic amines involves formation of an intermediate hydroxylamine, in the case of lidocaine–*N*-hydroxyxylidine.	The time of blood asmpling after lidocaine administration was not provided. Before lidocaine treatment, seven patients had adduct concentrations less than 50 ng 2,6-xylidine/g hemoglobin and one patient had a concentration between 50 and 100 ng/g. Another patient had a high level of adducts before treatment (423 ng 2,6-xylidine/g hemoglobin). After lidocaine treatment levels ranged from ~110-690 ng 2,6-xylidine/g hemoglobin. The increase of adducts from before to after lidocaine administration ranged from 93 to 636 ng 2,6-xylidine/g hemoglobin. The study shows that 2,6-xylidine-hemoglobin adducts are formed in humans following lidocaine treatment and result in measurable methemoglobinemia.	Bryant et al. (1994)

Table C-1. Metabolism Studies of Lidocaine in Humans and Experimental Animals (Continued)

Subjects	Dose	Compounds Detected	Remarks	Reference
3 Normal Human Subjects (Sex n.p.)	Oral dose of ^{3}H-labeled lidocaine hydrochloride (500 mg) containing 50 μCi of randomly tritiated lidocaine hydrochloride; duration n.p.	Determined the presence of several known metabolites, as well as a new metabolite, of lidocaine. Compounds detected were: Ethylamino-2,6-dimethylacetanilide [LID] Monoethylglycinexylidide [MEGX] 2,6-Dimethylaniline [XYL] *N*^{1}-Ethyl-2-methyl-*N*^{3}-(2,6-dimethylphenyl)-4-imidazolidinone [IMZ05]	Feces and urine were collected for 72 hr after dosing. After 72 hr, 50% of the radioactivity was recovered in the urine, with most of the radioactivity being excreted in the first 8 hr after dosing. The fraction composed of organic bases comprised 12% of the radioactivity found in the urine. Metabolites were not quantitated. The radioactive compounds in the urine samples were mostly conjugated since treatment with glucuronidase and sulfatase yielded insignificant activity in the base extracts.	Breck and Trager (1971)
3 Male Beagle Dogs	Oral administration with 2% lidocaine hydrochloride (10 mg/kg bw); duration n.p.	Lidocaine [LID] (2.0% of total lidocaine dose) Monoethylglycinexylidide [MEGX] (2.3%) Glycinexylidide [GX] (12.6%) 3-Hydroxylidocaine [3'-LIDOH] (6.7%) 3-Hydroxymonoethylglycinexylidide [3'-MEGXOH] (3.1%) 2,6-Xylidine [XYL] (1.6%) 4-Hydroxy-2,6-xylidine [4-XYLOH] (35.2%)	Metabolites were recovered in a 24-hr urine collection in the amounts noted in Column 3 of this table. The dog showed a higher amount of GX in the urine than humans, guinea pigs, or rats after a 24-hr urine collection.	Keenaghan and Boyes (1972)

Table C-1. Metabolism Studies of Lidocaine in Humans and Experimental Animals (Continued)

Subjects	Dose	Compounds Detected	Remarks	Reference
16 Dogs (Breed and Sex n.p.)	Infusion with lidocaine (0.2 mg/kg/min) for 5 min followed by continuous infusion of 0.8 mg/kg/min for 1.5 hr (n = 8) and 6 hr (n = 8).	Determined the concentrations of MEGX and GX in the plasma and myocardium after infusion.	The mean lidocaine, MEGX, and GX plasma concentrations after 1.5 hr of infusion were 2.1 ± 0.6 □g/mL, 0.5 ± 0.2 □g/mL, and 0.8 ± 0.3 □g/mL, respectively. The mean lidocaine, MEGX, and GX plasma concentrations after 6 hr of infusion were 2.1 ± 0.6 □g/mL, 1.1 ± 0.4 □g/mL, and 1.9 ± 0.5 □g/mL, respectively. The left ventricle/plasma ratio of lidocaine and GX were very similar at 1.5 hr (2.6 and 2.8, respectively) and the same at 6 hr (2.3). The left ventricle/plasma ratio of MEGX was 3.6 at 1.5 hr and 3.3 at 6 hr. The study showed that lidocaine metabolites accumulated over time in dogs as in humans and that there is no time-dependent delay in myocardial lidocaine accumulation.	Handel et al. (1982 abstr.)
6 Female Guinea Pigs	Oral administration of 1% lidocaine hydrochloride (20 mg/kg bw);	Lidocaine [LID] (0.5% of total lidocaine dose) Monoethylglycinexylidide [MEGX] (14.9%) Glycinexylidide [GX] (3.3%) 3-Hydroxylidocaine [3'-LIDOH] (0.5%) 3-Hydroxymonoethylglycinexylidide [3'-MEGXOH] (2.0%) 2,6-Xylidine [XYL] (16.2%) 4-Hydroxy-2,6-xylidine [4-XYLOH] (16.4%)	Metabolites were recovered in a 24-hour urine collection in the amounts noted in Column 3 of this table. Guinea pigs excreted a larger amount of unhydroxylated 2,6-xylidine than dogs, humans, or rats. The lower amount of the total lidocaine dose recovered (53.8%) was attributed to the possibility that the guinea pig may further metabolize 2,6-xylidine to 2-amino-3-methylbenzoic acid [AMBA].	Keenaghan and Boyes (1972)

Table C-1. Metabolism Studies of Lidocaine in Humans and Experimental Animals (Continued)

Subjects	Dose	Compounds Detected	Remarks	Reference
6 Female Sprague-Dawley Rats	Gavaged with 20 mg/kg bw of 1% lidocaine-HCl for comparative metabolite study; gavaged with 10 mg/kg of 1% ^{3}H-lidocaine hydrochloride for p.o. tissue distribution study; i.v. administration of 5 mg/kg bw of 1% ^{3}H-lidocaine hydrochloride for i.v. tissue distribution study	Lidocaine [LID] (0.2% of total lidocaine dose) Monoethylglycinexylidide [MEGX] (0.7%) Glycinexylidide [GX] (2.1%) 3-Hydroxylidocaine [3'-LIDOH] (31.2%) 3-Hydroxymonoethylglycinexylidide [3'-MEGXOH] (36.9%) 2,6-Xylidine [XYL] (1.5%) 4-Hydroxy-2,6-xylidine [4-XYLOH] (12.4%)	After gavage, the highest amounts of radioactivity were found in the intestine (47.5% of dose) at 4 hr, and in the stomach (13.7%), liver (11.7%), and kidney (2.0%) at 30 min. After i.v. administration of ^{3}H-lidocaine hydrochloride, tissue distribution was rapid as was evident by the fact that 5 min after injection <2.0% of the administered radioactivity was found in the blood. Most tissues reached their maximum level of lidocaine or lidocaine metabolites at 30 min, except for the intestine, which reached its peak between 2 and 4 hr. Biliary excretion after p.o. administration in the 24-hour recovery of bile averaged 28.5% of dose. Biliary excretion after i.v. administration in the 24-hr recovery of bile averaged 30.0% of dose. Metabolites were recovered in a 24-hr urine collection in the amounts noted in Column 3 of this table. After i.v. administration, the half-life of lidocaine in the plasma of rats was approximately 30 min, compared to about 90 min in man after i.v. administration (Boyes et al., 1971).	Keenaghan and Boyes (1972)
2 Male Sprague-Dawley Rats	i.v. injection into the femoral vein with ^{14}C-labeled lidocaine hydrochloride (4.2 mg/kg bw); duration n.p.	Determined biliary excretion of lidocaine	Bile was collected for 4 hr after administration of lidocaine. The amount of radiation detected in bile was 33.5% (range 29.9-37.0%) of the total dose. Lidocaine was metabolized quickly due to the fact that only traces of activity were detected with the same Rf value as the original compound. The carbon on the carbonyl group was labeled so that the recovered radioactivity would not be able to indicate the portion of the lidocaine metabolite that would result in 2,6-xylidine formation. The metabolites seemed to be more polar than the original starting compound, probably due to hydroxylation. The metabolites were probably conjugated with glucuronic acid and sulfate.	Ryrfeldt and Hansson (1971)

Table C-1. Metabolism Studies of Lidocaine in Humans and Experimental Animals (Continued)

Subjects	Dose	Compounds Detected	Remarks	Reference
Male Charles River CD Rats (Number n.p.)	i.p. 2,6-xylidine (900 mg/kg in corn oil) or i.p. lidocaine (120 mg/kg in saline)	Determined 2,6-xylidine-hemoglobin adducts after administration of lidocaine [LID] and 2,6-xylidine [XYL]	After 24 hours, ~0.84% of the dose (788 μg 2,6-xylidine/g hemoglobin) was covalently bound to hemoglobin after treatment with 2,6-xylidine. After lidocaine administration, ~0.027% of the dose (1.8 μg 2,6-xylidine/g hemoglobin) was found bound to hemoglobin.	Bryant et al. (1994)
Male Sprague-Dawley Rats (number n.p.)	i.p. injection with lidocaine hydrochloride (40 mg/kg bw); duration n.p.	The compounds detected were: 3-Hydroxymonoethylglycinexylidide [3'-MEGXOH] (major metabolite) 2,6-Xylidine [XYL] (minor metabolite) MEGX (minor metabolite) GX (minor metabolite) 4-Hydroxylidocaine [4'-LIDOH] (minor metabolite) 3-Hydroxylidocaine [3'-LIDOH] (minor metabolite)	The major metabolite detected was 3-hydroxymonoethylglycinexylidide. Minor quantities of 2,6-xylidine, MEGX, GX, 4-hydroxylidocaine, and 3-hydroxylidocaine were detected. In contrast to the Keenaghan and Boyes (1972) study, only minute amounts of 3-hydroxylidocaine were detected. The hydrolyzed metabolites were converted to pentafluorobenzoyl derivatives for determination by GC-MS.	Coutts et al. (1987)
3 Male Wistar Rats	i.p. administration of lidocaine hydrochloride (27 mg/kg bw); duration n.p.	Compounds detected in the 24-hr urine of rats were: 3-Hydroxylidocaine [3'-LIDOH] 4-Hydroxylidocaine [4'-LIDOH]	Analysis of the 24-hour urine from the rats showed that metabolism of lidocaine resulted in the formation of 3-hydroxy- (6-16% of dose) and 4-hydroxylidocaine (3-5% of dose) with only 3-hydroxylidocaine being excreted as a glucuronide conjugate. The other metabolites may be sulfate conjugates.	Thomas and Meffin (1972)

Table C-1. Metabolism Studies of Lidocaine in Humans and Experimental Animals (Continued)

Subjects	Dose	Compounds Detected	Remarks	Reference
In Vitro Studies				
Human Liver Slices from five donors	Incubated with lidocaine hydrochloride, MEGX, or xylidine in concentrations of 50, 100, and 250 µM for up to 4 hr	Monoethylglycinexylidide [MEGX] Glycinexylidide [GX] 4-Hydroxy-2,6-xylidine [4-XYLOH]	The xylidine concentration in the medium after 4-hr incubation with lidocaine hydrochloride (100 µM) or MEGX (100 µM) was very similar, 9.8 µM ± 2.1 and 7.9 µM ± 2.1. The mean media ratios of xylidine to MEGX after incubation with lidocaine were 1.1 after 1 hr and 1.0 after 4 hr. When media concentrations of lidocaine increased, MEGX and xylidine formation increased in a linear fashion. 4-Hydroxyxylidine increased after acid hydrolysis, which suggested the presence of its glucuronide conjugate. This study showed that xylidine may be formed directly as a result of hydrolysis of lidocaine as well as of MEGX.	Parker et al. (1996)
Rat Brain, Lung, Kidney, and Liver Microsomes from Sprague-Dawley Rats; Reconstituted system with pulmonary microsomes containing cytochrome P450 isozymes CYP2B1, CYP2C11, and CYP4B1	Concentration of lidocaine in the medium ranged from 0.2 to 2.0 mM; incubation of liver, lung, and kidney microsomes for 10 min; incubation of brain microsomes for 60 min; liver and lung microsomes were treated with phenobarbitol (PB)	Monoethylglycinexylidide [MEGX] 3-Hydroxylidocaine [3'-LIDOH] Methylhydroxylidocaine (Hydroxymethyllidocaine) [□-LIDOH]	Untreated and PB-treated pulmonary microsomes formed MEGX only at 0.87 ± 0.11 and 0.98 ± 0.21 nmol/min/mg of microsomal protein, respectively. Untreated and PB-treated liver microsomes formed mainly MEGX, with low rates of 3'-LIDOH and □-LIDOH formation. The rate of MEGX formation was 4.84 ± 1.31 nmol/min/mg in untreated and 11.38 ± 1.54 nmol/min/mg in PB-treated liver microsomes. A slow rate of formation of MEGX (0.024 ± 0.004 nmol/min/mg) and 3'-LIDOH (0.022 ± 0.001 nmol/min/mg) was determined in kidney microsomes. MEGX was the only metabolite formed by the P450 isozymes CYP2C11 (73.2 nmol/min/nmol P450) and CYP2B1 (74.1 nmol/min/nmol P450) when 1 mM lidocaine was used as a substrate. Antibodies against CYP2B1 completely inhibited MEGX formation in lung microsomes and inhibited MEGX formation by 70% in liver microsomes. There is evidence that CYP2B1 may be the sole enzyme that catalyzes the N-deethylation of lidocaine in rat pulmonary and renal microsomes. Lidocaine was not metabolized by brain microsomes.	Tanaka et al. (1994)

Table C-1. Metabolism Studies of Lidocaine in Humans and Experimental Animals (Continued)

Subjects	Dose	Compounds Detected	Remarks	Reference
Male Wistar Rat Lung, Liver, and Kidney Slices	Incubated with lidocaine (5 mM) for 3 hr (lung and kidney) or 1 hr (liver slices)	Monoethylglycinexylidide [MEGX]	No MEGX was detected in samples of rat kidney cortex; however, 5 pmol MEGX/3hr/µg protein was detected in rat kidney medulla slices. The rate of MEGX formation was 20 pmol/3hr/µg protein in rat lung slices and 450 pmol/3hr/µg protein in rat liver slices. Lidocaine metabolism in the rat lung was only about 5% that of hepatic metabolism. Renal cortex metabolism of other compounds was detected, so all the cortex slice samples were viable.	de Kanter et al. (1999)
Human Lung, Liver, and Kidney Slices	Incubated with lidocaine (5 mM) for 3 hr (lung and kidney) or 1 hr (liver slices)	Monoethylglycinexylidide [MEGX]	Incubation of lidocaine with human kidney slices gave ~20 pmol MEGX/3hr/µg protein in the cortex and ~10 pmol MEGX/3hr/µg protein in the medulla. Formation of MEGX with human lung slices ranged from around 10 to 50 pmol MEGX/3hr/µg protein. Formation of MEGX with human liver slices was ~90 pmol MEGX/3hr/µg protein. Lidocaine metabolism in the human lung was about 50% that of hepatic metabolism.	de Kanter et al. (1999)

Table C-1. Metabolism Studies of Lidocaine in Humans and Experimental Animals (Continued)

Subjects	Dose	Compounds Detected	Remarks	Reference
Rat Liver, Olfactory, and Respiratory Microsomes (9 Male Long-Evans Rats)	Incubation of microsomal protein (120 µg/mL) and reaction mixture with lidocaine (50-400 µM) for 30 min	Monoethylglycinexylidide [MEGX]	The metabolism of lidocaine to MEGX was studied in nasal microsomes due to its recent approval as a nasal drug for migraine headaches, evidence of extrahepatic metabolism, and the potential first-pass metabolism by abundant P450 enzymes contained in the nasal mucosa. K_M values (µM) for the metabolism of lidocaine by different microsomes were as follows: human liver (363.43), rat liver (304.33), rat olfactory (156.77), and rat respiratory (505.23). V_{max} values (µM/min) for the metabolism of lidocaine by different microsomes are as follows: human liver (0.23), rat liver (0.41), rat olfactory (0.54), and rat respiratory (0.09). Rat nasal microsomes had a much higher affinity for lidocaine than rat liver microsomes. The authors found it difficult to make a cross-comparison between human liver microsomes and rat microsomes since the human microsomes are pooled from multiple human donors. Rat olfactory microsomes had a much higher affinity for lidocaine than rat nasal respiratory or liver microsomes. The rat olfactory microsomes seemed to contain higher levels of CYP1A2 and 2B1 than found in the rat liver. The rat liver contained more CYP2C11 and 3A2 than the trace amounts detected in rat olfactory microsomes. Respiratory and olfactory mucosa each occupy 50% of the rat nasal cavity, while olfactory mucosa represents <10% of the surface of the human nose and respiratory mucosa makes up the rest (Bogdanffy et al., 1997; Harkema, 1990; Jafek et al., 1997). Both humans and rats express the pi form of glutathione *S*-transferase in the nasal cavity (Gervasi et al., 1991).	Deshpande et al. (1999)

Table C-1. Metabolism Studies of Lidocaine in Humans and Experimental Animals (Continued)

Subjects	Dose	Compounds Detected	Remarks	Reference
White New Zealand Male Rabbit Liver Homogenates (9000 *g* supernatant fraction); number n.p.	Incubation with lidocaine (5 mol)	Determined the presence and amount of 2-amino-3-methylbenzoic acid [AMBA] and other metabolites with lidocaine. The concentrations of metabolites as a percentage of lidocaine metabolized at 30 and 120 min were: Monoethylglycinexylidide [MEGX] (67.8%, 37.1%) Glycinexylidide [GX] (3.1%, 5.1%) 3-Hydroxymonoethylglycinexylidide [3'-MEGXOH] (1.6%, 1.1%) 3-Hydroxylidocaine [3'-LIDOH] (2.1%, 1.7%) 4-Hydroxylidocaine [4'-LIDOH] (0.4%, 0.4%) Xylidine [XYL] (7.3%, 35.5%) 4-Hydroxyxylidine [4-XYLOH] (4.1%, 7.9%) 2-Amino-3-methylbenzoic acid [AMBA] (0.2%, 0.5%) Proposed (but did not detect) these metabolites: 2,6-Dimethylnitrobenzene [$C_6H_3Me_2NO_2$] Lidocaine *N*-oxide [LID-*N*-Ox] 2,6-Dimethylnitrosobenzene [$C_6H_3Me_2NO$]	2-Amino-3-methylbenzoic acid was detected as a metabolite of lidocaine; its formation was found to be dependent on the presence of protein, NADPH, O_2, and soluble enzymes (non-microsomal). Doubling the protein content increased the amount of 2-amino-3-methylbenzoic acid formed, while substituting nitrogen for air decreased formation. 2-Amino-3-methylbenzoic acid was not formed when purified microsomes (non-soluble enzymes) were used alone. The major metabolites formed were monoethylglycinexylidide and xylidine, showing that N-dealkylation and amide hydrolysis are important pathways in the rabbit. A mean 84% of the dose was accounted for at 30, 60, 90, and 120 min of incubation, so it is likely that there may be other metabolites that were not detected in this assay. It was proposed that other metabolites may occur, such as a 2,6-dimethylnitrobenzene, 2,6-dimethylnitrosobenzene and lidocaine *N*-oxide, but may constitute only minor amounts of the administered dose. Nohmi et al. (1983) has shown that the proposed hydroxylamine of 2,4-xylidine has been detected as an *in vitro* product of incubation with rat liver 9000g supernatant.	Kammerer and Schmitz (1986)
Mouse Liver Slices	Incubated with ^{3}H-lidocaine (200 nmol)	2,6-Xylidine [XYL]	Detected concentrations of 2,6-xylidine rose slowly but steadily during the 60-min test period and leveled off at 50 nM at 60 min.	Åkerman et al. (1966)

Table C-1. Metabolism Studies of Lidocaine in Humans and Experimental Animals (Continued)

Subjects	Dose	Compounds Detected	Remarks	Reference
Human Liver Microsomes, S9 Fractions and Liver Homogenates from five individual patients	Inubations with lidocaine hydrochloride or MEGX (20-5000 M) for 30 min	Monoethylglycinexylidide [MEGX] 2,6-Xylidine [XYL] (Trace amounts) 4-Hydroxy-2,6-Xylidine [4-XYLOH]	MEGX was determined as the major metabolite after incubation with lidocaine in microsomes. Xylidine was detected in small amounts only when microsomes were incubated with >500 µM lidocaine (>10 times the toxic plasma level *in vivo*). The rate of MEGX and xylidine formation was linear with increasing lidocaine concentrations; however, the amount of xylidine and 4-hydroxyxylidine produced was ≤1% of the amount of MEGX. When lidocaine or MEGX concentrations were <500 µM, the amount of xylidine and 4-OH XYL were below the limit of quantitation (1 µM). Addition of UDPGA to the medium resulted in a greater rate of disappearance of 4-hydroxyxylidine, suggesting that 4-hydroxyxylidine may undergo conjugation with glucuronic acid. 4-Hydroxylidocaine was not quantitated due to its instability. No xylidine was detected when lidocaine (100 µM) was incubated with either human liver S9 fractions or whole liver homogenates. The results suggested that the enzyme primarily responsible for the hydrolysis of lidocaine may be labile in subcellular fractions. Data from incubation of lidocaine with S9 fractions and crude liver homogenates prepared from frozen liver tissue were qualitatively similar to those obtained with liver microsomes.	Parker et al. (1996)

Abbreviations: bw = body weight; F = female(s); hr = hour(s); i.m = intramuscular; i.p. = intraperitoneal; i.v. = intravenous; M = male(s); min = minute(s); mo = month(s); n.p. = not provided; p.o. = per oral; sec = second(s); wk = week(s)

Table C-2. Pharmacokinetics Studies of Lidocaine in Humans and Experimental Animals

Subjects	Dose	Remarks	Reference
In Vivo Studies			
3 Healthy Human Volunteers (Sex n.p.)	Oral administration of of lidocaine hydrochloride monohydrate (300 mg) given orally every 8 hr for 7 doses	Peak lidocaine concentrations were detected in blood samples from 20 to 60 min after dosing. Total clearance of lidocaine was 15.3, 15.0, and 15.4 mL/min/kg. The volume of distribution of lidocaine at steady state was 1.9, 1.3 and 3.61 per kg. Half-life of the terminal phase of elimination was 84, 89, and 149 min. Blood MEGX concentrations were comparable to those of lidocaine due to lidocaine's low oral availability and high renal clearance. In contrast, MEGX concentrations are much lower than lidocaine concentrations when lidocaine is administered intravenously. One subject had steady state concentrations of lidocaine 42% below those predicted. This study revealed that the first-pass effect was not saturable and that individual variations in lidocaine kinetics may change with repetitive administration.	Bending et al. (1976 abstr.)
Mother (23 wk pregnant) and two twin fetuses	i.v. administration of lidocaine hydrochloride (50 mg/hr for 282 hr; total: 14.1 g) while undergoing ritodrine therapy for the control of pre-term labor.	Mother was experiencing preterm labor and polyhydramnios and was treated with lidocaine because of heart arrhythmia as a result of ritodrine therapy. The twins died of respiratory distress and intracranial hemorrhage 12 and 14 days after birth. Plasma concentrations of lidocaine were determined at delivery. The maternal venous concentration of lidocaine was 1.6 µg/mL. Umbilical vein concentrations were 0.83 and 0.81 µg/mL. Amniotic fluid concentrations were 1.05 and 1.04 µg/mL. Umbilical vein/maternal vein ratios were 0.51 and 0.52. This result was similar to ratios between 0.48 and 0.69 obtained in other studies. There was a higher concentration of lidocaine in the amniotic fluid than was found in the fetal plasma but did not accumulate as much as the authors had assumed as a result of prolonged infusion. Because of fetal hypoxia and acidosis there is an increase in diffusion across the placenta as well as a greater accumulation of lidocaine in fetal plasma. Increased acidity of the gastric compartment may lead to greater absorption in gastric fluid, higher than lidocaine concentrations in the plasma. Gastric washout in neonates suspected of lidocaine intoxication may help to reduce the amount of lidocaine in serum due to swallowed lidocaine in amniotic fluid.	Banzai et al. (1995)
18 Healthy Human Volunteers (9M, 9F)	Topical application of 5% lidocaine ointment (Ortotidema) (5 g applied topically to a 100 cm^2 area of forearm = 250 mg of lidocaine) for 45 min	Using a highly sensitive bioassay, lidocaine was determined to persist in plasma for over 32-hr after a single topical application to the skin of human volunteers. Interassay and intra-assay precision and accuracy of the method used were ≤3.8%. Mean plasma concentrations of lidocaine peaked in increasing steadily until a peak of between 2.3–40.4 ng/mL was reached between 1 and 28 hours after application. It was evident that there was a wide deviation in each individual's ability to absorb lidocaine transdermally and distribute it in the plasma due to the wide variability in the amount of lidocaine present over the 32-hr observation period in each subject.	Dal Bo et al. (1999)

Table C-2. Pharmacokinetics Studies of Lidocaine in Humans and Experimental Animals (Continued)

Subjects	Dose	Remarks	Reference
Healthy Human Volunteers (M, number n.p.)	Topical dosing by placing a 2-cm^2 patch containing 46.1 mg lidocaine on gingival mucosa for 15 min. topical application of 5% lidocaine ointment (amount n.p.)	Serum blood concentrations of lidocaine were compared after application of the patch and the ointment. The maximum mean plasma level of lidocaine after application of the patch was 21 ng/mL after about 45 min. The mean half-life of elimination of lidocaine from the plasma was over 2 hr. Concentrations of lidocaine were detected for as long as 8 hr after application of the patch. The maximum plasma concentration of lidocaine after application of the patch was about 1/7 of that found after application of the 5% ointment.	Noven Pharmaceuticals (1997)
Healthy Humans (Sex and Number n.p.)	Topical dosing by placing a 2-cm^2 patch containing 46.1 mg lidocaine on gingival mucosa for 15 min; topical application of 50 mg of 5% lidocaine ointment; i.v. lidocaine (dose n.p.)	The peak plasma concentrations of lidocaine after application of the patch was 16.5 ± 7.9 ng/mL after 28.6 ± 12.9 min. The terminal half-life of lidocaine in plasma after application of the patch was 102 ± 25 min. The apparent dose of lidocaine after application of the patch averaged 1.55 ± 0.77 mg, compared with 3.77 ± 2.71 mg from the 5% ointment and 4.79 ± 0.79 mg from the given i.v. drug.	Noven Pharmaceuticals (1997)
Healthy Human Volunteers (16F, 14M)	Topical dosing from 2-cm^2 patch containing 46.1 mg lidocaine (topical site and duration n.p.)	The mean peak plasma concentrations were 27.2 ± 15.2 ng/mL at 45 ± 12.5 min after application. Mean peak concentrations were 31.5 ± 17.4 ng/mL in females and 22.2 ± 10.6 ng/mL in males.	Noven Pharmaceuticals (1997)

Table C-2. Pharmacokinetics Studies of Lidocaine in Humans and Experimental Animals (Continued)

Subjects	Dose	Remarks	Reference
6 Human Patients with Viral Hepatitis	i.v. injection of indocyanine green (0.5 mg/kg bw) in antecubital vein, followed by lidocaine hydrochloride (1 mg/kg bw) at the same site for 1 min	Patients were healthy in all other respects. During viral hepatitis the mean clearance of lidocaine was 13.0 mL/min/kg but increased to 20 mL/min/kg after infection. The mean initial volume of distribution of lidocaine was 3.1 L/kg during hepatitis infection and 2.0 L/kg after infection. The mean terminal $t_{1/2}$ for lidocaine was 160 min during infection and 90 min after infection. However, there was a noticeable interindividual variation in results that may have been explained by stage of infection at the time of testing, blood flow rate, or extraction ratios. One patient actually experienced a decrease in clearance and an increase in terminal half-life of lidocaine. There was no significant difference in plasma binding of lidocaine. The mean lidocaine fraction unbound was 0.56 ± 0.08 during illness and 0.49 ± 0.12 after recovery. These results were not obtained with indocyanine green. The clearance of indocyanine green decreased during hepatitis infection without a significant change in the volume of distribution. It was concluded that pharmacokinetic parameters of disposition of indocyanine green and lidocaine during hepatitis were unpredictable, even though they both are highly dependent on hepatic blood flow and clearance. Lidocaine disposition may be impaired in individuals with acute hepatic dysfunction. It has been shown in a previous study that the extraction ratio of lidocaine after first pass of blood through the liver was ~0.70 (Stenson et al., 1971) and the extraction ratio of indocyanine green was between 0.63 and 0.88 (Caesar et al., 1961; Cherrich et al., 1960).	Williams et al. (1976)
5 Perfused Single Human Placental Cotyledons	Lidocaine (500 µg) in 10 µL of distilled water; 25 mg of antipyrene in 100 µL of distilled water used as a reference compound	The transfer of lidocaine across the placenta was compared to bupivacaine. To account for differences in placental characteristics, values were normalized with respective antipyrene data. Maternal disappearance of lidocaine ($t_{1/2}$ = 33.0 ± 9.8 min) was not as rapid as that of bupivacaine ($t_{1/2}$ = 26.3 ± 4.8 min). This half-life was the initial phase of a biphasic semilogarithmic maternal plasma concentration curve. After 2 hr, the mean amount of lidocaine transferred across the placenta was 22.1 ± 2.21%. The fetal/maternal plasma lidocaine concentration ratio after 2 hr was 0.90 ± 0.09. The mean peak lidocaine concentration immediately after the initial bolus was 2.47 ± 0.42 µg/mL. After 2 hr, maternal and fetal compartment concentrations of lidocaine were almost at equilibrium (~1.25 and 1.15 µg/mL, respectively).	Ala-Kokko et al. (1995)

Table C-2. Pharmacokinetics Studies of Lidocaine in Humans and Experimental Animals (Continued)

Subjects	Dose	Remarks	Reference
24 Human Volunteers (22M, 2F)	i.v. injection (femoral artery) of prilocaine and lidocaine (alone and together; dose and route n.p.) with ammonium chloride given orally to acidify urine and sodium bicarbonate given by i.v. infusion to alkalize the urine.	The excretion of both lidocaine and prilocaine were determined to be sensitive to the pH of urine. Higher clearance values were observed when the urine was acidic and dropped to almost zero when the urine was alkaline. If more acid was given then clearances increased. Prilocaine and lidocaine were excreted by non-ionic diffusion. Lidocaine exhibited a lower clearance rate than prilocaine. The venous blood/arterial blood ratio was 0.73 ± 0.003 for lidocaine and was significantly different than that of prilocaine (0.47 ± 0.03). The lower ratio for prilocaine may be one reason why its toxicity is lower than that of lidocaine.	Eriksson (1966)
20 Patients (15 M and 5 F), 5 mo old to 6 yr old;	Epidural infusion with an initial bolus of 1% lidocaine hydrochloride (5 mg/kg bw) for 1 min, followed by continuous infusion of lidocaine hydrochloride (2.5 mg/kg/hr)	The range of AAG in all patients was between 34.0 and 81.0 mg/dL. There was no correlation between age and AAG concentrations, steady-state lidocaine concentrations, or accumulation rates of MEGX. There was a weak inverse correlation between AAG concentration and GX; however, there was a very significant inverse correlation between MEGX and AAG concentration. Interpatient variability of AAG concentrations was most significant in patients younger than 9 mo. There was a significant direct relationship between the steady-state concentration of lidocaine and plasma AAG concentrations. The effect of plasma protein concentrations and MEGX is important since MEGX has approximately 80% of the convulsant potential of lidocaine itself (Blumer et al., 1973). The authors recommended that both lidocaine and MEGX concentrations in plasma should be monitored in children during continuous epidural anesthesia. If this monitoring is difficult then, at least, MEGX should be monitored in patients with low AAG plasma concentrations.	Kakiuchi et al. (1999)

Table C-2. Pharmacokinetics Studies of Lidocaine in Humans and Experimental Animals (Continued)

Subjects	Dose	Remarks	Reference
8 Term Babies (5F, 3M), 6 Rheumatoid Arthritis Patients (6F), 7 Metastatic Cancer Patients (4F, 3M), and 6 Healthy Subjects (2F, 4M)	Blood and serum were obtained from the subjects and analyzed for protein concentration	Serum protein concentrations varied considerably between patient types. The cord blood from the term babies contained 5.1 ± 0.2 g/100 mL albumin and 0.41 ± 0.05 mg/mL α_1-acid glycoprotein. The serum of normal patients contained 5.4 ± 0.4 g/100 mL albumin and 0.78 ± 0.07 mg/mL α_1-acid glycoprotein. The serum of the arthritis patients contained 5.1 ± 0.2 g/100 mL albumin and 1.48 ± 0.10 mg/mL α_1-acid glycoprotein. The serum of the cancer patients contained 4.0 ± 0.3 g/100 mL albumin and 2.93 ± 0.45 mg/mL α_1-acid glycoprotein. From this study the authors proposed a free intermediate model which proposes that some bound lidocaine may be able to enter tissue via a "free intermediate mechanism." Rapid transport of lidocaine into tissue, such as the liver, may represent transport by the free intermediate mechanism. The albumin-bound drug did not enter the brain. It was recommended that existing pharmacokinetics models should take into account the transport of protein-bound drugs into peripheral tissues similar to what is known to occur in the liver.	Pardridge et al. (1983)
1 Beagle Dog (Sex n.p.)	i.v. bolus of lidocaine hydrochloride (0.94 mg/kg bw)	Plasma lidocaine concentrations peaked at 200 ng/mL 15 min after administration and decreased linearly to about 10-15 ng/mL 2 hr after administration. The half-life was 0.86 hr.	Kang et al. (1999)
40 Near-term Pregnant Rabbits (Strain n.p.)	i.v. administration of ^{3}H-labeled lidocaine (0.6 mg/kg bw) in another group of rabbits.	There was no significant difference in the bupivacaine- and lidocaine-treated animals with respect to pH (7.52 and 7.53) and oxygen pressure (169 and 153 mm Hg), but the arterial carbon dioxide values were slightly higher in the bupivacaine group (28.2 ± 1.12 mm Hg) than in the lidocaine-treated group (24.5 ± 1.02 mm Hg). At 2 min, the maternal heart/blood ratio in the lidocaine group (4.1) was 4 times higher than in the bupivacaine-treated group (1.03), and at 5 min. it was twice as high (2.1 and 1.2). The fetal/maternal blood ratios of bupivacaine were 0.37 (2 min) and 0.41 (5 min), and fetal/maternal blood ratios of lidocaine were 0.64 (2 min) and 0.82 (5 min). The fetal heart/blood ratios were constant over time in both groups, with the lidocaine group having 1.06 and bupivacaine having a ratio of only a 0.60 ratio. The fetal brain/blood ratios behaved the same with the ratio in bupivacaine-dosed rabbits being 0.43 and the lidocaine group exhibiting a ratio of 1.09. The fact that the ratios of fetal brain/blood and fetal heart/blood were constant with time in both groups indicated an early equilibrium between fetal tissue and blood. The lower fetal heart/blood and fetal brain/blood ratios in the bupivacaine group suggest an advantage to using bupivacaine rather than lidocaine in obstetric analgesia. The lower fetal/maternal blood concentrations in the bupivacaine-dosed group indicated slower placental transfer or permeability of bupivacaine when compared to lidocaine.	Hollmén (1973)

Table C-2. Pharmacokinetics Studies of Lidocaine in Humans and Experimental Animals (Continued)

Subjects	Dose	Remarks	Reference
Sprague-Dawley Rats (>72F)	Injection of 1% ^{14}C-labeled lidocaine (0.05 mL) and/or ^{14}C-labeled prilocaine into the tip of the tongue (n=72); i.m. injection of above doses into sciatic nerve (number n.p.)	At 2,4, and 8 min after injection, more prilocaine than lidocaine was detected in the tongues (n=48). Because lidocaine has a vasodilatory effect, the two anesthetics were administered together in 24 rats to determine if any changes in absorption occur. When the two were administered together there was no difference in the concentrations of the individual anesthetics over time. In an area that is not as richly vascularized as the tongue, the rate of disappearance of lidocaine and prilocaine, when administered alone, were not statistically different.	Åkerman et al. (1966)
Sprague-Dawley Rats (60F)	i.m. injection of 1% ^{14}C-labeled lidocaine (10 mg/kg bw) into the sciatic nerve pocket	Concentrations of recovered radioactivity after lidocaine administration peaked in the lungs (20.7 µg/g) 10 min after dosing, and peaked in the kidney (22.7 µg/g), spleen (16.6 µg/g), brain (13.6 µg/g), and liver (6.8 µg/g) 30 min after dosing.	Åkerman et al. (1966)

Abbreviations: bw = body weight; F = female(s); hr = hour(s); i.m = intramuscular; i.p. = intraperitoneal; i.v. = intravenous; M = male(s); min = minute(s); n.p. = not provided

APPENDIX D

Metabolism and Pharmacokinetics of Mepivacaine

APPENDIX D

This appendix contains the detailed studies of the metabolism and pharmacokinetics of mepivacaine. The metabolites and proposed metabolites of mepivacaine are listed in the compounds measured column of **Table D-1**. A key to the codes used for the metabolites of mepivacaine is given below along with the organization of Appendix D.

Key to Mepivacaine Metabolite Codes

Code	Chemical Name
MEP	Mepivacaine
3'-MEPOH	3'-Hydroxymepivacaine; 1-Methylpipecolo-3'-hydroxy-2,6-xylidide
4'-MEPOH	4'-Hydroxymepivacaine; 1-Methylpipecolo-3'-hydroxy-2,6-xylidide
6-oxo-MEP	1-Methyl-6-oxopipecolo-2',6'-xylidide
6-oxo-4/5-MEP	*N*-(2,6-Dimethylphenyl)hydroxy-1-methyl-6-oxo-2-piperidinecarboxamide
6-oxo-PPX	6-Oxopipecolo-2',6'-xylidide
3',4'-oxy-MEP	1-Methylpipecolo-3',4'-dihydro-3',4'-epoxy-2',6'-xylidide
N-MEPOH	1-Methylpipecolo-*N*-hydroxy-2',6'-xylidide
PPX	Pipecoloxylidide; Demethylmepivacaine; PPX

Table D-1. Metabolism Studies of Mepivacaine in Humans and Experimental Animals

Subjects	Dose	Compounds Determined	Remarks	Reference
4 Male Adult Subjects	Rapid i.v. injection of mepivacaine hydrochloride (1.5 mg/kg bw; total: 110-134 mg). One subject received a second dose 48 hr after the first.	Determined urinary and biliary excretion of mepivacaine and it metabolites in 11- to 30-hr urine samples. Compounds and their amounts determined were in urine: 3'-Hydroxymepivacaine [3'-MEPOH] (14.5% of dose) 4'-Hydroxymepivacaine [4'-MEPOH] (11.2%) Proposed intermediates: 1-Methylpipecolo-3',4'-dihydro-3',4'-oxy-2',6'-xylidide 3,4-oxy-MEP [3',4'-oxy-MEP] 1-Methylpipecolo-*N*-hydroxy-2',6'-xylidide [*N*-MEPOH]	Mean 11- to 30-hr urine concentrations of 3'-hydroxymepivacaine and 4'-hydroxymepivacaine were 15881 μg (14.5% of the dose) and 12293 (11.2%), respectively. The range of concentrations of the metabolites was very wide (e.g., 8963-29078 for 3'-hydroxymepivacaine). The excretion of metabolites was not dose dependent. It was proposed that 3'-hydroxymepivacaine, but not 4'-hydroxymepivacaine, is formed directly from an epoxide intermediate, 1-methylpipecolo-3',4'-dihydro-3',4'-oxy-2',6'-xylidide. 4'-hydroxymepivacaine is thought to be a product of another primary *N*-hydroxy intermediate, 1-methylpipecolo-*N*-hydroxy-2',6'-xylidide.	Meffin and Thomas (1973)
1 Female Adult Subject (with bile duct drainage tube as a result of pancreatitis and cholycystolithiasis)	Rapid i.v. injection of mepivacaine hydrochloride (1.3 mg/kg bw)	Determined urinary and biliary excretion of mepivacaine metabolites in 10-hr urine samples. Compounds and amounts determined in the urine were: 3'-Hydroxymepivacaine [3'-MEPOH] (9.9% of the dose) 4'-Hydroxymepivacaine [4'-MEPOH] (7.6%)	No hydroxylated metabolites were found in the bile. The 24-hr urine concentrations of 3'-hydroxymepivacaine and 4'-hydroxymepivacaine were 7350 μg (9.9% of the dose) and 5670 μg (7.6% of the dose), respectively.	Meffin and Thomas (1973)
3 Human Males	Oral administration of mepivacaine hydrochloride (50 mg)	4'-Hydroxymepivacaine [4'-MEPOH] (12.5-17.5%) 3'-Hydroxymepivacaine [3'-MEPOH] (12.5-17.5%) 2',6'-Pipecoloxylidide [PPX] (1.0%)	Analysis of 24-hr urine samples revealed that metabolism of mepivacaine in humans results in the formation of almost equal amounts of 4'-hydroxy- and 3'-hydroxymepivacaine comprising about 25-35% of the total dose. This is in contrast to metabolism in the rat which resulted in about 60% of the dose being converted to ring-hydroxylated mepivacaine. These metabolites are probably almost entirely excreted as glucuronide conjugates. PPX was determined to comprise a mean 1.0% of the mepivacaine dose. Less than 1.5% of the dose is excreted as unchanged mepivacaine.	Thomas and Meffin (1972)

Table D-1. Metabolism Studies of Mepivacaine in Humans and Experimental Animals (Continued)

Subjects	Dose	Compounds Determined	Remarks	Reference
One Healthy Human Male Subject	p.o. administration of mepivacaine hydrochloride (250 mg)	Determined the metabolites of mepivacaine in an overnight (12 hr) urine collection. The metabolites detected were: Mepivacaine [MEP] 1-Methyl-6-oxopipecolo-2',6'-xylidide [6-oxo-MEP] 1-Methylpipecolo-3'-hydroxy-2',6'-xylidide [3'-MEPOH] 1-Methylpipecolo-4'-hydroxy-2',6'-xylidide [4'-MEPOH] 1-Methyl-hydroxy-6-oxopipecolo-2',6'-xylidide [6-oxo-4/5-MEP] 6-Oxopipecolo-2',6'-xylidide [6-oxo-PPX]	Formation of 6-oxopipecolo-2',6'-xylidide, 1-methyl-6-oxopipecolo-2',6'-xylidide, and 1-methyl-?-hydroxy-6-oxopipecolo-2',6'-xylidide involves the conversion to a neutral species. Hydrolysis of these three compounds would form amino acids that would escape detection in extraction procedures used up until the publication of this study. It was estimated that these three new piperidones together comprised not more than 10% of the administered dose of mepivacaine found in a 12-hr urine	Meffin et al. (1973a)
Adult Male Volunteers (Number n.p.)	i.v. dose of 50 mg (acidified urine) or 100 mg (non-acidified urine) mepivacaine hydrochloride into antecubital vein with or without ammonium chloride taken 24 hr before experiment to regulate urinary pH	Determined metabolite excretion in 30 hour urine collection from subjects with normal and acidic urinary pH. Detected: 2,6-Pipecoloxylidide [PPX] 1-Methyl-3'-hydroxy-2,6-pipecoloxylidide [3'-MEPOH] 1-Methyl-4'-hydroxy-2,6-pipecoloxylidide [4'-MEPOH]	Since mepivacaine has a pK_a of 7.6, acidification of the urine should increase its rate of urinary excretion of mepivacaine. The subjects with acidified urine (pH 5.5-6.0) excreted twice as much mepivacaine per mg administered than subjects in the normal uncontrolled urinary pH (5.0-7.2) group (10% and 5%, respectively). Differences in urine pH did not effect the excretion of metabolites of mepivacaine. The excretion of pipecoloxylidide was not affected by pH, due to the fact that the degree of ionization is not greatly altered over the pH rage studied; pipecoloxylidide has a pK_a of 8.6. Greater than 99% of each of the two phenolic metabolites of mepivacaine were excreted as glucuronide conjugates in adult males.	Meffin et al. (1973b)

Table D-1. Metabolism Studies of Mepivacaine in Humans and Experimental Animals (Continued)

Subjects	Dose	Compounds Determined	Remarks	Reference
9 Women in Labor and their male neonates	Epidural dose of mepivacaine hydrochloride (250-580 mg); other drugs such as morphine, pethidine, diazepam, and hyoscine-*N*-butyl bromide were also administered.	Determined metabolite excretion in the urine of neonates for 30 hr after delivery. Male babies were studied for ease of sample retrieval. Compounds determined were: Mepivacaine [MEP] Pipecoloxylidide [PPX] 3'-Hydroxymepivacaine [3'-MEPOH] 4'-Hydroxymepivacaine [4'-MEPOH]	Greater than 99% of the two phenolic metabolites of mepivacaine were excreted as glucuronide conjugates in neonates. Neonatal urinary pH ranged from 5.5 to 6.7. At delivery, maternal venous plasma concentrations of mepivacaine and PPX ranged from 3.65-5.50 μg/mL and <0.10-0.38 μg/mL, respectively. Umbilical artery plasma concentrations of mepivacaine and PPX ranged from 0.97-3.20 μg/mL and <0.10-0.66 μg/mL, respectively. Umbilical venous plasma concentrations of mepivacaine and PPX ranged from 1.10-3.30 μg/mL and <0.10-0.60 μg/mL, respectively. The ratio of pipecoloxylidide to mepivacaine in the neonate and adult groups (above study) was 0.323 and 0.455, respectively. The ratios of 3'-hydroxy- and 4'-hydroxymepivacaine were much greater in adults (3.547 and 2.775, respectively) than in neonates (0.033 and 0.048, respectively). This indicates that aromatic hydroxylation is not present or not efficient enough to produce measurable concentrations of metabolites in neonates. Ninety percent of the total amount of mepivacaine found in the urine of neonates was recovered in the first 24 hr after delivery. It must be taken into consideration that the neonatal concentrations of these metabolites may be affected by the fact that local anesthetics, their metabolites, and glucuronide conjugates may cross the placenta.	Meffin et al. (1973b)
3 Male Wistar Rats	i.p. administration of ^{14}C-labeled mepivacaine (13.5 mg/kg)	3'-Hydroxymepivacaine [3'-MEPOH] (50% of the dose) Mepivacaine [MEP] Pipecoloxylidide [PPX] (Trace amounts)	Examination of the 24-hour urine samples showed that 50% of the dose was excreted as 3'-hydroxymepivacaine after glucuronidase treatment. Only trace amounts of unchanged mepivacaine were detected in the 24-hr urine samples. Trace amount of PPX were found in the urine of rats, like humans. 4'-Hydroxymepivacaine was not detected at all as a metabolite in rats. 60% of the dose was excreted in the urine of rats and 1.5-8.1% in the next 72 hr. The feces contained 5.3-15.6% of the dose (1-72 hr).	Thomas and Meffin (1972)

Table D-1. Metabolism Studies of Mepivacaine in Humans and Experimental Animals (Continued)

Subjects	Dose	Compounds Determined	Remarks	Reference
4 Healthy Male Volunteers (21-22 yr old)	i.v. dose of mepivacaine (n = 3; 43.46 mg each) for 1 min	Determined the extent of PPX formation in plasma and excretion in urine after administration of mepivacaine and bupivacaine. Mepivacaine [MEP] (16% of dose found in 24-hr urine collection) Pipecoloxylidide [PPX] (5%)	After administration of mepivacaine, 6.96 ± 1.23 mg (16% of the dose) was unchanged and 0.54 ± 0.04 mg (1.2%) was excreted as PPX in the 24-hr urine collection. Between 10 min and 2 hr after administration, the whole blood concentration of mepivacaine decreased from about 4 to 1 □g/mL. Since such small amounts of the dose of mepivacaine was excreted as PPX, and 50% of the PPX dose was excreted unchanged, N-dealkylation is not as important for the metabolism of these two anesthetics as it is for lidocaine. N-dealkylation may be inhibited by steric interference by the piperidine ring.	Reynolds (1971)
In Vitro Studies				
Liver Slices from Adult Male Rats	Incubation with ^{14}C-labeled mepivacaine (dose n.p.) for 95 min	Determined metabolism after incubation of slices with air, 100% O_2, and 100% N_2. Chloroform, water, and $^{14}CO_2$ fractions were used to determine the extent of metabolism.	Mepivacaine was oxidatively metabolized. Some metabolism occurred in air and none occurred in nitrogen (anaerobically). More radioactivity was recovered in the chemical fractions of the chloroform phase (55.2% in O_2, 85.6% in air, and 97.1% in N_2) than in the water phase (24.5%, 74%, and 1.3%, respectively). The CO_2 extraction phase after incubation in 100% O_2 exhibited the highest amount of radioactivity (15.9%), when compared to incubation in air (2.3%) or N_2 (0.1%).	Hansson et al. (1965)

Abbreviations: bw = body weight; hr = hour(s); i.p. = intraperitoneal; i.v. = intravenous; min = minute(s); n.p. = not provided; p.o. = per oral; yr = year(s)

Table D-2. Pharmacokinetics Studies of Mepivacaine in Humans and Experimental Animals

Subjects	Dose	Study Objective	Remarks	Reference
5 Healthy Male Volunteers	i.v. infusion with mepivacaine hydrochloride (250 mg)	Non-metabolite study	Mean plasma concentrations of mepivacaine peaked at 3.5 µg/mL after 10 min and decreased to under 1.0 µg/mL after 4 hr. The mean total body clearance was 0.70 L/min and the terminal half-life was calculated to be 125 min. These results were similar to ones reported by Tucker and Mather (1975) of a terminal half-life of 114 min and a clearance of 0.78 L/min.	Arthur et al. (1979)
150 Pregnant Mothers and their Fetuses	Pudendal block with 1% mepivacaine (20 mL) with or without epinephrine (5 µg/mL)	Determined maternal plasma concentrations of mepivacaine and placental transfer to the fetus with and without epinephrine.	The median *S*-mepivacaine concentration in maternal venous blood was 1.18 µg/mL (range 0.26-3.17 µg/mL) in the plain group and 0.86 µg/mL (range 0.03-2.52 µg/mL) in the group treated with epinephrine immediately after birth. The median S-mepivacaine concentration in umbilical venous blood was 0.42 µg/mL (range <0.05-1.54 µg/mL) and 0.37 µg/mL (range <0.05-1.25 µg/mL), respectively. There was no difference in newborn Apgar scores between the plain and epinephrine group; however, a prolongation of the second stage of labor was observed with epinephrine which has been linked to a significantly increased tendency for fetal acidosis. Eighty-five percent in the epinephrine group and 91% in the plain group experienced good or excellent pain relief.	Schierup et al. (1988)

Table D-2. Pharmacokinetics Studies of Mepivacaine in Humans and Experimental Animals (Continued)

Subjects	Dose	Metabolites	Remarks	Reference
12 Pregnant Women and their Fetuses	Paracervical block with 20 mL of 1% (200 mg, n=5), 1.5% (300 mg, n=1), and 2% (400 mg, n=6) concentrations of mepivacaine; range 2.7 to 6.4 mg/kg maternal body weight	Determined maternal and fetal plasma mepivacaine concentrations as well as fetal pH.	Six fetuses born to 5 mothers in the 400 mg dose group and 1 in the 300 mg dose group exhibited bradycardia and a decrease in pH (mean of –0.115) after the paracervical block. The mean plasma concentration of mepivacaine in mothers receiving 400 mg mepivacaine was 4.47 µg/mL (range 2.1-5.6 µg/mL) and 1.86 µg/mL (range 1.4-2.4 µg/mL) in mothers receiving 200 mg. The mean maximum mepivacaine concentration in the blood of the six fetuses that experienced bradycardia was 3.07 µg/mL (range 0.5-8.3 µg/mL). The mean maximum concentration in the fetuses experiencing no bradycardia was 1.52 µg/mL (range 0.4-2.5 µg/mL). One fetus had a mepivacaine concentration of 8.3 µg/mL 12 min after block with 300 mg mepivacaine, while the corresponding maternal concentration was was 2.2 µg/mL. The fetal pH in this fetus was 7.20at about 10 min. A correlation exists between the severity of fetal bradycardia and the extent of fetal pH decrease after paracervical block (Teramo, 1969). No signs of toxicity were observed in any of the mothers	Teramo and Rajamäki (1971)
29 Female Sprague-Dawley Rats	Intraarterial infusion of mepivacaine hydrochloride (1 mg/mL; 0.2 mL/min) for 30 or 45 min; concomitantly with pilocarpine hydrochloride (0.25 mg/mL) given to induce salivation	Compared blood and saliva concentrations of mepivacaine	The concentration of mepivacaine in saliva was studied in order to determine the feasibility of using a non-invasive salivary assay for the safe and effective monitoring of mepivacaine blood concentrations in newborns. There was no clear relationship between the saliva concentrations of mepivacaine and blood concentrations. Saliva (and blood) concentrations of mepivacaine were 4.79 ± 0.84 µg/g (8.57 ± 1.07 µg/g) in the 30-min infusion group and 14.30 ± 4.64 µg/g (8.10 ± 0.85 µg/g). Mepivacaine saliva-to-blood ratios were 0.64 ± 0.13 and 2.13 ± 0.48 µg/g in the 30- and 45-min infusion groups, respectively.	Gans et al. (1980)

Table D-2. Pharmacokinetics Studies of Mepivacaine in Humans and Experimental Animals (Continued)

Subjects	Dose	Metabolites	Remarks	Reference
35 Non-pregnant Adult Female Sprague-Dawley Rats and 29 Neonates	s.c injection of mepivacaine hydrochloride (25 or 50 mg/kg bw)	Compared neonatal and adult brain-to-blood ratios in rats after dosing.	The blood and brain concentrations of unbound mepivacaine base in neonates were much higher than in the adult rats; however, the blood-to-brain ratios of mepivacaine in the two groups were not significantly different. In adults, the brain (and blood) concentrations of mepivacaine were 5.16 ± 0.54 µg/g (2.61 ± 0.30 µg/g) in the 25 mg/kg dose group and 5.31 ± 0.52 µg/g (2.73 ± 0.38 µg/g) in the 50 mg/kg dose group 15 min after dosing. In neonates, brain (and blood) concentrations were 15.50 ± 2.2 µg/g (8.76 ± 1.5 µg/g) in the 25 mg/kg dose group and 21.98 ± 2.2 µg/g (11.26 ± 1.3) in the 50 mg/kg dose group 15 min after dosing. The adult blood-to-brain ratios were 2.58 ± 0.39 and 3.48 ± 1.6 in the 25 mg/kg and 50 mg/kg dose groups, respectively. The neonatal blood-to-brain ratios of mepivacaine were 2.01 ± 0.26 and 2.54 ± 0.44 in the 25 mg/kg and 50 mg/kg dose groups, respectively.	Gans et al. (1980)

Table D-2. Pharmacokinetics Studies of Mepivacaine in Humans and Experimental Animals (Continued)

Subjects	Dose	Metabolites	Remarks	Reference
Adult Male Rats (Strain and Number n.p.)	i.v. administration of ^{14}C-labeled mepivacaine (2 mg)	Mepivacaine Demethylmepivacaine [PPX00] p-hydroxylated product	The appearance of radioactivity in the urine of rats was rapid, with approximately 15% of the administered radioactivity recovered after 1 hr in 2 rats and 55% after 24 hr. Seventy-two hr after administration of mepivacaine 59.1% of the total radioactivity was detected in the urine and 4.3% in the feces. Six hours after administration 51.4-56.5% of the radio-labeled dose was excreted in the bile with 27.5-32.4% excreted in the first half hour after administration. In mice, 10.5-11.4% of the dose was found in expired air over an 8-hr period. The majority of the radioactivity found in the urine and bile was associated with metabolites. Most of the radioactivity in the bile (50% of the administered mepivacaine) is probably absorbed by the intestine and excreted in the urine due to the small amount of radioactivity found in the feces. Eighty to 82% of the radioactivity in the bile and 76-85% in the urine could be extracted as glucuronide conjugates. An increase in urinary pH resulted in a much larger recovery of radioactivity. A major route of metabolism is by N-demethylation and to a small extent hydroxylation at the 4-position. The acute i.v. LD50 in mice was approximately 40 mg/kg for mepivacaine and estimated to be 63 mg/kg for demethylmepivacaine and 122 mg/kg for the *p*-hydroxy metabolite of mepivacaine (unpublished study).	Hansson et al. (1965)
3 Adult Mice (Strain and Sex n.p.)	i.v. administration of ^{14}C-labeled mepivacaine (0.4 mg)	Determined respiratory radiocarbon dioxide		

Table D-2. Pharmacokinetics Studies of Mepivacaine in Humans and Experimental Animals (Continued)

Subjects	Dose	Metabolites	Remarks	Reference
4 Male Sprague-Dawley Rats	i.v. injection of ^{14}C-labeled mepivacaine hydrochloride (6.6 mg/kg bw) into the femoral vein	Polar metabolites	Bile was collected for 6 hr after administration of mepivacaine. The amount of radiation detected in bile was 54.3% (range 51.4-56.5%) of the total dose. Mepivacaine was metabolized quickly due to the fact that none was detected in the bile. The carbon on the methyl group of the amino moiety was labeled so that the recovered radioactivity would not be able to indicate the portion of metabolites that would result in 2,6-xylidine formation. The metabolites seemed to be more polar than the original starting compound. The authors also stated that many compounds such as amines may undergo further conjugation with ß-glucuronidase and sulfatase.	Ryrfeldt and Hansson (1971)
Male White Mice (Strain and Number n.p.)	i.v. injection of ^{14}C-labeled mepivacaine (30 mg/kg bw) into the tail	Determined tissue distribution of mepivacaine after i.v. injection using whole body autoradiographs	Concentrations were determined in an ether and a water phase in different tissues. The highest concentrations of radioactivity were found in the liver (11.7% of dose in both phases), kidney (3.5%), brain (2.4%), and submaxillary glands (0.6%) at 5 min after i.v. administration. At 20 min post-injection the percentage accumulation was relatively the same; however, the increased presence of water soluble compounds indicated the accumulation of metabolites mostly in the liver and kidney but also in the submaxillary gland (0.3%). One hour after injection the accumulation of water soluble radioactivity was considerably higher than ether phase radioactivity in the liver, kidney, and intestine. Presence in the intestine of ether and water phase radioactivity was 3.5% of dose and 9.8%, respectively, indicating a high degree of biliary excretion. No water soluble radioactivity was detected in the brain at any time. Results were similar after s.c. administration. Transplacental transfer was determined to take place by simple diffusion without active uptake. Radioactivity concentrations were lower in fetal than maternal tissues; radioactivity was not localized in any tissue.	Kristerson et al. (1965)
Male White Mice (Strain and Number n.p.)	s.c. injection of of ^{14}C-labeled mepivacaine (30 mg/kg); duration n.p.	Determined tissue distribution of mepivacaine after s.c. injection using whole body autoradiographs. Animals killed up to 96 hr after injection.		
Male White Mice (Strain and Number n.p.)	i.v. injection of of ^{14}C-labeled mepivacaine (30 mg/kg bw) into the tail for 2 min	Determined metabolic products of mepivacaine in different tissues after i.v. injection. Animals killed up to 96 hr after injection.		
Pregnant Female White Mice (Strain and Number n.p.)	i.v. injection of ^{14}C-labeled mepivacaine (40 mg/kg bw) in the tail; duration n.p.	Determined placental transfer of mepivacaine after i.v. administration. Animals killed up to 24 hr after injection.		

Abbreviations: bw = body weight; hr = hour(s); i.v. = intravenous; min = minutes(s); n.p. = not provided; s.c. = subcutaneous

APPENDIX E

Metabolism and Pharmacokinetics of Prilocaine

APPENDIX E

This appendix contains detailed descriptions of the studies on metabolism and pharmacokinetics of prilocaine. The metabolites and proposed metabolites of prilocaine are listed in the compounds measured column of **Table E-1**. A key to the codes used for the metabolites of prilocaine is given below along with the organization of Appendix E.

Key to Metabolites of Prilocaine

Codes	Chemical Name
PRI	□-Propylamino-2-methylpropionanilide; Prilocaine
TOL	*o*-Toluidine
4'-PRIOH	*p*-Hydroxyprilocaine
6-TOLOH	*o*-Hydroxytoluidine; 6-Hydroxy-*o*-toluidine
4-TOLOH	*p*-Hydroxytoluidine; 4-Hydroxy-*o*-toluidine
N-PrALA	*N*-*n*-Propylalanine

Table E-1. Metabolism Studies of Prilocaine in Humans and Experimental Animals

Subjects	Dose	Compounds Determined	Remarks	Reference
5 Healthy Medical Students (24-28 yr, 4 M and 1F)	s.c. infiltration in the thigh with prilocaine (20 mg/kg bw); duration n.p.	The mean percent of the total dose of unconjugated metabolite detected in 24-hr urine collections *o*-Hydroxytoluidine [6-TOLOH] (2.7% of prilocaine dose; 15.6 mg) *p*-Hydroxytoluidine [4-TOLOH] (34.2%; 254.8 mg) *p*-Hydroxyprilocaine [4'-PRIOH] *o*-Toluidine [TOL] (0.75%; 5.02 mg) Prilocaine [PRI]	Similar plasma concentration curves were seen in all subjects with respect to time and degree of changes in the concentration of *p*-hydroxytoluidine and methemoglobin with peak concentrations of *p*-hydroxytoluidine occurring between 4 and 5 µg/mL around 4 to 5 hr after administration. These concentrations decreased exponentially until leveling at <1 µg/mL around 20 hr after administration. The methemoglobin curve paralleled that of *p*-hydroxytoluidine with its peak 1 hr after the peak of *p*-hydroxytoluidine. In four subjects, 4 µg/mL *p*-hydroxyotoluidine in plasma corresponded to a methemoglobin concentration of 10-15%. In the fourth subject, 4µg/mL *p*-hydroxytoluidine in plasma corresponded to a methemoglobin concentration of about 2%. *o*-Toluidine or *o*-hydroxytoluidine were not detected in plasma.. *p*-Hydroxytoluidine was mainly excreted in urine as a conjugate with only 0.03% of the prilocaine dose excreted in the unconjugated form. Nitroso or hydroxylamino metabolites of prilocaine were not detected in the blood or urine.	Hjelm et al. (1972)

Table E-1. Metabolism Studies of Prilocaine in Humans and Experimental Animals (Continued)

Subjects	Dose	Compounds Determined	Remarks	Reference
12 Human Neonates (5 M and 7 F; Mean age 31.6 wk)	Topical application EMLA (0.5 g) applied to 5-cm^2 area of the heel for 30 min 4x /day	Determined plasma concentrations of prilocaine and two of its metabolites. Lidocaine [LID] Prilocaine [PRI] *o*-Toluidine [TOL]	Plasma concentrations of lidocaine and prilocaine were determined at a maximum of 6 to 12 hr after first application, respectively. The highest concentrations of lidocaine and prilocaine in one patient were 0.230 and 0.223 mg/L, respectively, 6 hr after application of EMLA. Eighteen hours after application of lidocaine-prilocaine cream, low concentrations of lidocaine and prilocaine were detected in one and six patients, respectively. There was no significant difference between methemoglobin concentrations after dosing and baseline concentrations. Methemoglobin concentrations were 0.2 to 1.1% after application of EMLA cream compared to baseline concentrations of 0.1 to 0.7%. Plasma concentrations of *o*-toluidine were below the detection limit of 0.025 mg/L. All methemoglobin concentrations were below the defined safety parameter of 5.0%. It was concluded that it was safe to apply EMLA at the recommended dosage, up to four times a day, in healthy preterm neonates; however, it was recommended that further studies were needed to assess the safety of use for more than 24 hr.	Essink-Tebbes et al. (1999)
1 Female Rat	s.c injection of ^{14}C-prilocaine (total radioactive counts injected was 809,900)	Metabolites were speculated to be: o-Toluidine [TOL] *N*-*n*-propylalanine [N-PrALA]]	The excretion of radioactivity was 41,270 counts (5.0% of the total dose) in expired air and 169,092 (23.0%) in urine over a 54-hr collection period. Of the 23% recovered in urine, 21% was recovered in the first 22 hr. Three hours after injection, 8 radioactive spots were found with paper chromatography from urine samples; one had the same Rf value as *N*-*n*-propylalanine hydrochloride. The kidney can affect decarboxylation after hydrolysis.	Geddes (1965, 1967)

Table E-1. Metabolism Studies of Prilocaine in Humans and Experimental Animals (Continued)

Subjects	Dose	Compounds Determined	Remarks	Reference
4 Healthy Cats of Both Sexes (Strain and Number of Each Sex n.p.)	i.v. administration of 2.0% solutions of (*D*)-(□)- and (*L*)-(+)-prilocaine (25 mg/kg) over a 15-minute period into femoral vein	Determined plasma concentrations of (*D*)-(□)- and (*L*)-(+)-prilocaine and *o*-toluidine after intravenous and subcutaneous administration of racemic prilocaine. Metabolites detected in plasma were: (*D*)-(–)-Prilocaine [(–)-PRI] (*L*)-(+)-Prilocaine [(+)-PRI] *o*-Toluidine [TOL]	The selective metabolism of the enantiomers of prilocaine and their effect on formation of methemoglobinemia were studied. The plasma concentration of (*D*)-(–)-prilocaine was lower than that of (*L*)-(+)-prilocaine during the entire test period (80 min). (*D*)-(–)-Prilocaine could not be detected at 50 min post-administration and (*L*)-(+)-prilocaine after 80 min. Two cats treated with (*D*)-(–)-prilocaine had a mean peak plasma *o*-toluidine concentration of 9.9 µg/mL and for (*L*)-(+)-prilocaine, the mean peak o-toluidine concentration was 7.0 µg/mL 15 min after administration. All dose groups (*D*-, *L*-, and *DL*-) experienced formation of methemoglobin; however, the rate of methemoglobin formation was more rapid with the (*D*)-form. Methemoglobin concentrations peaked at 1 hr post-injection with the (*DL*)-(±)-and (*D*)-(–) forms of prilocaine and 3 hr with the (*L*)-(+) form, yet there was no significant difference in the maximum concentrations of methemoglobinemia in the two dosed groups (14% and 12, respectively). The rate of methemoglobin formation in the group dosed with the (*DL*)-(±)- form of prilocaine was between that of the (*D*)- and (*L*)-prilocaine dosed groups, but the mean maximum methemoglobin concentration in blood was 10%.	Åkerman and Ross (1970)
19 Healthy Cats of Both Sexes (Strain and Number of Each Sex n.p.)	i.v. administration of 2.0% solutions of (*D*)-(□), (*L*)-(+), and (*DL*)-(±)-prilocaine (all 20 mg/kg) at a rate of 1 ml/min into femoral vein.	Determined the formation of methemoglobin after injection of racemates and racemic mixtures.		

Table E-1. Metabolism Studies of Prilocaine in Humans and Experimental Animals (Continued)

Subjects	Dose	Compounds Determined	Remarks	Reference
6 Full Term Male Newborn Piglets (Number n.p.)	i.v. bolus injection of prilocaine and lidocaine (both 25 mg) on day 1; 3 days later EMLA (25 mg lidocaine and 25 mg prilocaine per gram) cream was topically applied to penile area under occlusion for 60 min	*o*-Toluidine [TOL]	The results recorded here were taken from one piglet. Blood plasma and urine samples were collected 30, 60, and 120 min after injection and topical application. The HPLC assay limit of quantitation was 20 ng/mL. Following i.v. administration of lidocaine and prilocaine, peak concentrations were detected at 30 min. Peak concentrations were 2066 ng/mL for lidocaine and 632 ng/mL for prilocaine. A peak *o*-toluidine level of 243 ng/mL was also observed 30 min after i.v. injection. Eight hr after i.v. administration, lidocaine, prilocaine, and *o*-toluidine concentrations had decreased linearly to 110, 20, and 50 ng/mL, respectively. After application of EMLA cream to penile area, peak concentrations of lidocaine and prilocaine were 140 ng/mL and 39 ng/mL, respectively, detected at 30 min. Two hours after dermal application, concentrations of lidocaine and prilocaine had decreased to below the limit of quantitation of the assay. *o*-Toluidine could not be detected at any time after penile application. There was considerable formation of *o*-toluidine in plasma after i.v. administration, but only marginal formation after penile application. Bioavailabiltity was 3.0% for lidocaine and 5.0% for prilocaine.	Klein et al. (1994)

Table E-1. Metabolism Studies of Prilocaine in Humans and Experimental Animals (Continued)

Subjects	Dose	Compounds Determined	Remarks	Reference
23 Newborn Male Piglets (n=21)	Topical application of of EMLA cream (1 g) (25 mg lidocaine and prilocaine) applied to penile area or i.v. administration of the same dose (25 mg prilocaine and 25 mg lidocaine) followed by topical treatment after a washout period.	*o*-Toluidine [TOL]	The mean bioavailability of prilocaine (n=6) was 6.1 ± 9.5% (range 0-24.4%) and lidocaine (n=7) was 3.9 ± 4.4% (range 0-13%). The mean production of *o*-toluidine after penile application of EMLA when compared to i.v. prilocaine administration was 1.6 ± 1.7% (0-4.2%). The mean maximum methemoglobin level after i.v. administration of prilocaine (n=11) was 1.3 ± 0.7% (0.9-3.0%) and after penile application (n=10) was 1.2 ± 0.4% (range 0.7-2.0%). The methemoglobin level was significantly elevated above baseline after i.v. administration (p=0.01) but not after penile application of EMLA (p>0.05). The bioavailability of prilocaine and lidocaine after penile application was low. There was marginal production of o-toluidine and methemoglobin concentrations did not reach clinical significance. There is a wide margin of safety with EMLA cream. The study was funded by Astra Pharmaceuticals (Canada).	Taddio et al. (1994)
In Vitro Studies				
Mouse Liver Slices	200 nM ^{3}H-Prilocaine	*o*-Toluidine [TOL]	^{3}H-labeled prilocaine (200 mμM) produced o-toluidine very rapidly, 125 mμM in 20 min, but this level dropped to 100 mμM after 60 min. The authors concluded that the decrease in the amount of detected o-toluidine may indicate that a further metabolic transformation may occur with this compound.	Åkerman et al. (1966)
Mouse Liver Slices	Incubated with ^{3}H-prilocaine (200 mμmol) for 60 min; some mice pretreated with SKF 525A, i.p. with 25 mg/kg	*o*-Toluidine [TOL]	The concentrations of *o*-toluidine rose sharply to a maximum concentration of 125 mμM 20 min after administration and decreased to about 100 mμM at 60 min. The formation of metabolites by liver slices was not affected by the pretreatment of mice with SKF 525A, a microsomal enzyme inhibitor.	Åkerman et al. (1966)

Table E-1. Metabolism Studies of Prilocaine in Humans and Experimental Animals (Continued)

Subjects	Dose	Compounds Determined	Remarks	Reference
Liver Homogenates and Slices from different species (mice, rats, guinea pigs, rabbits, and cats) (strains n.p.); Lung and Kidney Homogenates from cats and rabbits (strains n.p.)	Incubated with ^{14}C-prilocaine (200 nmol); homogenates incubated for 30 min and slices incubated for 20 min	Determined the extent of metabolism of prilocaine by liver slices and homogenates. Compounds detected were: *N*-Propylalanine [*N*-PrALA] *o*-Toluidine [TOL]	Determined that prilocaine was metabolized by hydrolysis of the amide linkage. The formation of aromatic, radioactive metabolites from prilocaine was significantly more rapid than with lidocaine. Lung and kidney homogenates from cats readily metabolized prilocaine as well as lidocaine; however, rabbit homogenates from lung and kdney only metabolized prilocaine. Rabbit liver homogenates and slices appeared to have the greatest metabolic activity for both prilocaine and lidocaine, followed by guinea pig, mouse, rat, and cat liver.	Åkerman et al. (1966)
Liver Homogenates and Slices from Mice, Rabbits, and Cats	Incubation with ^{14}C-labeled prilocaine (carbonyl labeled; 400 µmol/mL for 60 min in homogenates and 133 µmol/mL for 30 min in slices)	Determined the rate of *in vitro* hydrolysis	The rate of hydrolysis of the enantiomers and a racemic mixture of prilocaine in homogenates increased in the following order: (*L*)-(+)-prilocaine, *DL*-(±)-prilocaine, and (*D*)-(–)-prilocaine. The liver of rabbits exhibited more hydrolytic activity than the livers of cats and mice. Because the soluble fraction of liver homogenates had no such activity, the enzymes responsible for the hydrolysis of prilociane were solely in the microsome fraction, with a high selectivity for the (*D*)-(–)-prilocaine form. The fraction hydrolyzed was ≤20% of the amount of the (*L*)-(+)-prilocaine form.	Åkerman and Ross (1970)
Rabbit Liver Microsomes	Incubated with ^{14}C-labeled prilocaine (carbonyl labeled; 400 µmol/mL) for 60 min			

Table E-1. Metabolism Studies of Prilocaine in Humans and Experimental Animals (Continued)

Subjects	Dose	Compounds Determined	Remarks	Reference
Slices of Rat Cerebral Cortex, Liver, and Kidney	Incubation with ^{14}C-prilocaine (Dose n.p.) for 3.5 hr	Determined *in vitro* metabolism of prilocaine [PRI]	The metabolism of prilocaine only occurred in the liver (3.8-5.6% of radioactivity) and the kidney (0.8%). The affinity for prilocaine was for the liver, kidney, and cerebral cortex, in ascending order. One unidentified metabolite was detected in the kidney slices and 3 unidentified metabolites were detected in liver slices after 1.5 hr with paper chromatography. None of the compounds was *L*-*N*-*n*-propylalanine	Geddes (1965, 1967)

Abbreviations: bw = body weight; F = female(s); hr = hour(s); i.p. = intraperitoneal; i.v. = intravenous; M= male(s); min = minute(s); n.p. = not provided; s.c. = subcutaneous; yr = year(s)

Table E-2. Pharmacokinetics Studies of Prilocaine in Humans and Experimental Animals

Subjects	Dose	Remarks	Reference
5 Healthy Male Volunteers (24-35 yr)	i.v. infusion with 250 mg (0.97 mmol) of prilocaine hydrochloride	Mean plasma concentrations of prilocaine peaked at 2.0 µg/mL after 10 min. and decreased to under 0.1 µg/mL after 2 hr, and the mean total body clearance was 2.84 L/min. The terminal half-life was calculated to be 93 min. The mean value for hepatic blood flow in a normal population is about 1.7 L/min, which is less than all of the calculated blood flow values from the individuals in this study. The authors concluded that the increased rate of elimination may be due to extrahepatic metabolism of prilocaine.	Arthur et al. (1979)
47 Infants (age 1-74 days; 36M, 11F)	Topical application of EMLA cream (5% lidocaine and prilocaine) on a 4- to 5-cm^2 area of the back of the hand (50 mg) or cubital area (50 mg) for 60-70 min; application of placebo cream in controls (n=23)	Before treatment methemoglobin concentrations in the infants ranged from 0.67-1.57% in the EMLA group and 0.63-1.43% in the placebo group. After treatment, methemoglobin concentrations ranged from 0.50-2.53% in the EMLA group and 0.50-1.53% in the placebo group between 0.5-18.0 hr. In the time interval between 3.5 and 13 hr, there was a significant difference in mean methemoglobin concentrations between the EMLA and placebo groups with a mean of 1.27 and 0.95, respectively. One sample in the EMLA group (2.53%) had a methemoglobin level higher than the reference value of 2% (2.53%). It was concluded that 1 g of 5% EMLA cream was safe when applied to the intact skin of term neonates less than three months of age.	Brisman et al. (1998)
10 Healthy Human Volunteers (5M, 5F)	Dermal application of 10 g EMLA cream (5.0% prilocaine and lidocaine) to 100-cm^2 area of the face or forearm under occlusion for 2 hr	Mean plasma concentrations of the anesthetics peaked at 2 to 2.5 hr following application of EMLA cream to the face, with lidocaine peaking at 150 ng/mL and prilocaine at 58 ng/mL. The maximum level of lidocaine after application to the lower arm was seen at 5 hr (18 ng/mL); prilocaine was below the detectable limit (<5 ng/mL).	Juhlin et al. (1989)
40 Male Neonates	Epicutaneous application of EMLA cream (5.0% prilocaine and lidocaine) or 30% lidocaine cream (1 mL) to the prepuce under occlusion for 1 hr	Management of pain in neonates during circumcision was better in the group receiving EMLA cream than in the 30% lidocaine group. The EMLA dosed group had the smallest increase in heart rates and blood pressure when compared to the lidocaine and control groups, which was considered a good indicator of pain response in infants. Both topical anesthetics were recommended over local injection or dorsal penile nerve block because of their ease of application, limited sytemic absorption, tolerance by patients, and elimination of vascular complications, stress, and pain. Therapeutic concentrations of EMLA (5-12 mg/kg) can be achieved with 1-2 g of the 5% cream. The superior pain management of EMLA cream in this study may be due to its hydrophobicity (lipophilicity), which may slow dermal absorption and allow more drug to accumulate at the site of application.	Woodman (1999)

Table E-2. Pharmacokinetics Studies of Prilocaine in Humans and Experimental Animals (Continued)

Subjects	Dose	Remarks	Reference
13 Healthy Human Volunteers; 8 Patients with psoriasis; and 3 Female Patients with dermatitis	Dermal application of 4-6 g of EMLA cream (5.0% lidocaine and prilocaine) to 25 cm^2 of the lower arm under occlusion for 1 hr	When EMLA was applied to the forearm of healthy volunteers, concentrations of prilocaine and lidocaine in the general circulation were below the detectable limit within 3 hr (<10 ng/mL). However, both lidocaine and prilocaine were detected at 2 to 3 hr from a vein that drained the site of application, and the prilocaine level was about 10-20% lower than the level of lidocaine. When EMLA was applied to lesions of the skin of patients with psoriasis or dermatitis, detectable concentrations of lidocaine (16-450 ng/mL) were seen in all patients (n=10) and prilocaine (20-11,870 ng/mL) in seven patients at 1 hr. In the draining vein, lidocaine and prilocaine were measurable at 1 hr and were found to be 2-90 times higher than concentrations in the general circulation. Concentrations of lidocaine and prilocaine in the draining vein were highest in atopic dermatitis patients (10,000-13000 ng/mL; 1000 times higher than in healthy patients). Prilocaine concentrations were 10-50% of lidocaine concentrations in the general circulation. Complete anesthesia was achieved much sooner in the patients with psoriasis and dermatitis (15 min) when compared to normal individuals (60 min); however, anesthesia dimished more rapidly in patients with skin conditions. The lower concentrations of prilocaine at all times when compared to lidocaine may be attributed to prilocaine's low plasma binding, high tissue affinity, and more rapid metabolism in the liver.	Juhlin et al. (1989)
24 Human Volunteers (22M, 2F)	i.v. injection into femoral artery of prilocaine and lidocaine (both separately and together) with ammonium chloride given to acidify urine and sodium bicarbonate given to alkinalize the urine.	The excretion of both lidocaine and prilocaine was determined to be sensitive to the pH of the urine. Higher clearance values were observed when the urine was acidic and dropped to almost zero when the urine was alkaline. If more acid was given, then clearances increased. Prilocaine and lidocaine were excreted by non-ionic diffusion. Prilocaine exhibited a higher clearance rate than lidocaine. The venous blood/arterial blood ratio was 0.73 ± 0.003 for lidocaine and 0.47 ± 0.03 for prilocaine. This lower ratio for prilocaine may be one reason why its toxicity is lower than that of lidocaine.	Erikson (1966)

Table E-2. Pharmacokinetics Studies of Prilocaine in Humans and Experimental Animals (Continued)

Subjects	Dose	Remarks	Reference
Near-term Pregnant Sprague-Dawley Rats (Number n.p.)	i.v. dose into the femoral vein with ^{14}C-prilocaine (carbonyl labeled; 6 mg/kg; ~6.23 counts/min)	Pregnant rats were sacrificed at 1, 5, 15, and 60 min and whole body radiograms and scintillation counting were used to determine distribution. Distribution was found to be similar to that of lidocaine (Katz et al., 1968) except that higher counts were seen at 1 and 2 min in this study compared to peak concentration in the liver at 15 min in the previous study. Prilocaine was detected in the placenta, amniotic fluid, and the fetus. Prilocaine concentrations in the placenta and fetus were much higher than in the maternal blood with blood/placenta and blood/fetus ratios of 0.26 ± 0.16 and 0.31 ± 0.18, respectively, at 1 min. The blood/placenta and blood/fetus ratios decreased to 0.08 ± 0.02 and 0.10 ± 0.02, respectively, at 15 min. The placenta/fetus ratios remained relatively the same but with slight fluctuations ranging from 1.18 ± 0.14 at 1 min and 1.33 ± 0.28 at 15 min. It was apparent by the constancy of the placenta/fetal ratios that the fetus and placenta reach a rapid equilibrium in rats. High concentrations were found in the kidney, liver, lung, heart, bowel wall, bone marrow, brain, and salivary glands.	Katz (1969)
Sprague-Dawley Rats (>72F)	Injection of 1% ^{14}C-labeled lidocaine (0.05 mL) and/or ^{14}C-labeled prilocaine into the tip of the tongue (n=72); i.m. injection of above doses into sciatic nerve (number n.p.)	At 2,4, and 8 min after injection, more prilocaine than lidocaine was detected in the tongues (n=48). Because lidocaine enhances local blood circulation (vasodilation) more than prilocaine, the two anesthetics were administered together in 24 rats to determine if any changes in absorption occur. When the two were administered together, there was no difference in the concentrations of the individual anesthetics over time. In an area that is not as richly vascularized as the tongue, the rate of disappearance of lidocaine and prilocaine, when administered alone, was not statistically different.	Åkerman et al. (1966)
23 Male Wistar Rats	Lung perfused with 2.0 µg/mL of prilocaine; liver perfused with 2, 10, and 100 µg/mL to determine liver clearance rates.	Closed system lung clearance for prilocaine, bupivacaine, and mepivacaine was measured and compared to liver clearance rates in perfused lung and liver. Single-pass uptake of prilocaine was measured. The closed system pulmonary clearance was 0.27 ± 0.04 mL/g • min (22.3 ± 3% of hepatic activity). Single-pass retention resulted in a 60% decrease in the maximum concentrations of prilocaine in venous pulmonary plasma when compared to controls. The mean residence time of prilocaine in the first-pass lung was increased by 40%. The isolated perfused rat liver exhibited the same clearance rate at low (2 µg/mL) and intermediate (10 µg/mL) doses (1.3 ± 0.1 mL/g /min); however, at high (100 µg/mL) doses, the hepatic clearance dropped to half (0.7 ± 0.1 mg/g/min). This decrease in hepatic clearance was probably due to enzyme saturation but was not seen with bupivacaine and mepivacaine. Extrahepatic elimination of prilocaine was detected, but it was no higher than that seen for mepivacaine (12%) or bupivacaine (16%). Clearance values in the lung were 0.3 mL/min, or about 20% of hepatic capacity. The lung did retain substantial amounts of prilocaine on first pass, which may help to buffer large prilocaine doses.	Geng et al. (1995)

Table E-2. Pharmacokinetics Studies of Prilocaine in Humans and Experimental Animals (Continued)

Subjects	Dose	Remarks	Reference
Mice (DSS) (number n.p.)	i.p. injection of ^{14}C-labeled 1.0% prilocaine (1.0%)	The amout of amine in the body of mice decreased from 10 mg/kg at initiation of test to 2.3 mg/kg 20 min later. The concentrations of amine (2.5 mg/kg) was not significantly affected by pre-treatment with SKF 525, a microsomal enzyme inhibitor. This is in contrast to significant inhibition of lidocaine metabolism with pretreatment.	Åkerman et al. (1966)
Sprague-Dawley Rats (60F)	i.m. injection of 1% ^{14}C-labeled prilocaine (10 mg/kg bw) into the sciatic nerve pocket	The general pattern of distribution of prilocaine in tissues was simillar to that of lidocaine except that prilociane concentrations were significantly higher. Concentrations of recovered radioactivity after prilocaine administration peaked in the lungs (37.0 µg/g) 10 min after dosing, and peaked in the kidney (28.0 µg/g), spleen (19.3 µg/g), brain (18.1 µg/g), heart (10.9 µg/g), and liver (7.3 µg/g) 30 min after dosing.	Åkerman et al. (1966)
15 Healthy Full-term Male Piglets (2.2-6.6 kg)	Topical application of either 1 g of EMLA cream (25 mg lidocaine and 25 mg prilocaine) to the penile region under occlusion for 1 hr; i.v. injection of lidocaine hydrochloride (25 mg) and prilocaine hydrochloride (25 mg) through a superficial vein over 1 min; or both EMLA and i.v. bolus with the second treatment after an average washout period of 4 days	Some of the data for this study are incomplete due to the deaths of 6 pigs attributed to respiratory failure from the use of pentobarbital anesthesia. Anesthesia was changed to halothane and no further deaths were reported. Bioavailabilities for lidocaine and prilocaine after topical application (n=8) were 4.0 ± 4.7% (range 0-13.6%) and 7.2 ± 5.7% (range 0-14.5%), respectively. Topical application of EMLA resulted in mean peak plasma concentrations of 28.09 ng/mL for lidocaine and 54.27 ng/mL for prilocaine 0.5 hr after application and 13.23 ng/mL for *o*-toluidine 1 hr after application. Mean methemoglobin concentrations in the topically dosed group (0.98 ± 0.37%) did not differ from baseline concentrations. Mean methemoglobin concentrations in the i.v. bolus dose group rose significantly from 0.95 ± 0.41% at baseline to 1.23 ± 0.64% at the peak (6 hr). Elimination half-lives after i.v. injection were 1.9 ± 0.7 hr for lidocaine, 1.4 ± 1.0 for prilocaine, and 5.4 ± 4.7 hr for *o*-toluidine. Clearance after i.v. injection was 26.6 ± 15.5 mL/min/kg for lidocaine and 111.4 ± 75.0 mL/min/kg for prilocaine.	Gazarian et al. (1995)

Abbreviations: bw = body weight; F = female(s); hr = hour(s); i.m. = intramuscular; i.p. = intraperitoneal; i.v. = intravenous; M = male(s); min = minute(s); n.p. = not provided

APPENDIX F

Metabolism and Pharmacokinetcs of Ropivacaine

APPENDIX F

This appendix contains the detailed studies of the metabolism and pharmacokinetics of ropivacaine. The metabolites and proposed metabolites of ropivacaine are listed in the compounds measured column of **Table F-1**. A key to the codes used for the metabolites of ropivacaine is given below along with the organization of Appendix F.

Key to Ropivacaine Metabolite Codes

Code	Chemical Name
(*S*)-ROP	Ropivacaine
(*S*)-PPX	Pipecoloxylidide
(*S*)-3'-ROPOH	3'-Hydroxyropivacaine
(*S*)-4'-ROPOH	4'-Hydroxyropivacaine
□-(*S*)-ROPOH	(*S*)-2-hydroxymethylropivacaine
(*S*)-3'-PPXOH	3'-Hydroxy-2',6'-pipecoloxylidide
(*S*)-PIP-AMBA	(*S*)-2-Carboxyropivacaine; (*S*)-Pipecolylaminomethylbenzoic acid

Table F-1. Metabolism Studies of Ropivacaine in Humans and Experimental Animals

Subjects	Dose	Compounds Determined	Remarks	Reference
6 Healthy Males	i.v. infusion of ^{14}C-labeled ropivacaine hydrochloride monohydrate (50 mg) in the forearm for 15 min	Mean concentrations of the detected metabolites in 96-hr urine collection was: 3'-Hydroxyropivacaine [(*S*)-3'-ROPOH] (36.9% of total dose) 2'-Hydroxymethylropivaccaine [(*S*)-□-ROP] (18.5%) Pipecoloxylidide [(*S*)-PPX] (2.8%) 3'-Hydroxypipecoloxylidide [(*S*)-3'-ROPOH] (2.2%) Ropivacaine [ROP] (1.0%) 4'-Hydroxyropivacaine [(*S*)-4'-ROPOH] (0.4%)	In six healthy humans, ropivacaine was extensively metabolized, with only 1.0 ± 0.6% of the dose excreted unchanged in the urine. The total radioactivity excreted in the urine was 86.3% of the dose, while 7.5% was excreted in the feces. The urinary excretion of radioactivity from ^{14}C-labeled ropivacaine in humans (86% of dose in 96 hr) is higher than that in rats (~41%) and dogs (63%), but similar to urinary excretion in pregnant rabbits (92%). The mean elimination half-life of ropivacaine was 2.0 hr; however, the mean elimination half-life of total radioactivity was 5.4 ± 2.9 hr (range 3.2-10.4 hr). The longer elimination time of total radioactivity was due to metabolites. The mean peak plasma level of ropivacaine was 5.5 ± 2.4 µM (range was 2.5-8.2 µM) 0-5 min after infusion. Detectable concentrations of radioactivity were seen for up to 14 hr in 4 subjects and up to 24 hr in 2 subjects. No 2,6-xylidine was detected in the urine. No racemization of metabolites was detected.	Halldin et al. (1996)

Table F-1. Metabolism Studies of Ropivacaine in Humans and Experimental Animals (Continued)

Subjects	Dose	Compounds Determined	Remarks	Reference
12 Healthy Volunteers (6M, 6F)	i.v. infusion with ropivacaine (40 mg) for 20 min either alone or with oral fluvoxamine (25 mg) or ketoconazole (100 mg) 2X/day for 2 days	The compounds determined in 24-hr urine collections and their mean amounts were: Ropivacaine [ROP] (≤1%) 2,6-Pipecoloxylidide [(*S*)-PPX] (1%) 3'-Hydroxyropivacaine [(*S*)-3'-ROPOH] (39%)	The groups treated with fluvoxamine and ketoconazole, inhibitors of CYP1A2 and CYP3A4, respectively, showed a decrease in the amount of the metabolites 2,6-pipecoloxylidide and 3'-hydroxyropivacaine in plasma. Fluvaxamine and ketoconazole inhibited clearance of ropivacaine by 68% and 15%, respectively. Administration of fluvoxamine strongly enhanced urinary excretion of (*S*)-PPX and inhibited that of 3'-hydroxyropivacaine, while the administration of ketoconazole increased urinary excretion of 3'-hydroxyropivacaine and inhibited formation of PPX. The mean plasma concentration of PPX after administration of ropivacaine alone was 16.6 mg/L 8 hr after the start of infusion. The mean terminal elimination half-life of PPX in plasma was 8.8 ± 2.8 hr in the group dosed with ropivacaine alone. After administration of fluvoxamine and ketoconazole, the mean PPX concentrations in plasma 8 hr after the start of infusion were 77.1 and 4.1 mg/L, respectively.	Arlander (1998)
28 Human Subjects (Sex n.p.)	Continuous epidural infusion of ropivacaine (30 mg/hr for urine analysis and 20 mg/hr for plasma analysis) for 72 hr	Determined the concentration of ropivacaine and its metabolites in (urine) and {plasma} Ropivacaine [ROP] (4.7 □M) {4.9 □M} 3'-Hydroxyopivacaine [(*S*)-3'-ROPOH] (118 □M) 2'-Hydroxymethylropivacaine [(*S*)-□-ROP] (trace) Pipecoloxylidide [(*S*)-PPX] (23.2 □M) {1.5 □M} 3'-Hydroxypipecoloxylidide [(*S*)-3'-PPXOH] (10.0 □M)	This was basically a study of an analytical technique for the quantitative determination of ropivacaine metabolites. Plasma and urine were analyzed. Analysis of urine from humans dosed with ropivacaine revealed the metabolites at left in urine and plasma.	Arvidsson et al. (1999)

Table F-1. Metabolism Studies of Ropivacaine in Humans and Experimental Animals (Continued)

Subjects	Dose	Compounds Determined	Remarks	Reference
11 Patients (3F, 8M; undergoing elective orthopedic hip or knee surgery)	Post-operative epidural infusion with ropivacaine (2 mg/mL) at a rate of 6 mL/hr for a mean duration of 108 ± 22 min	The compounds determined in 82-hr urine samples and the median amounts were: Ropivacaine [ROP] (1.4%) 3'-Hydroxyropivacaine [3'-ROPOH] (16%) PPX (10%)	The recovery of ropivacaine, 3'-hydroxyropivacaine, and PPX in the urine of the patients was 20-39% of the administered dose of ropivacaine. There was a wide range in the urinary excretion of ropivacaine (0.5-4.1%), 3'-hydroxyropivacaine(7-36%), and PPX (2-20%). In one patient with liver disease, PPX recovery in the urine (20%) was almost 3 times greater than recovery of 3'-hydroxyropivacaine (7%).	Scott et al. (1997)
22 Male Volunteers	i.v. infusion of 150 µmol ropivacaine over 15 min (n=6); rectal administration of ropivacaine (300 µmol) in gel form (n=16)	Determined racemisation of urinary metabolites of ropivacaine. The metabolites detected were: (S)-3'-Hydroxyropivacaine [(*S*)-3'-ROPOH] (S)-Pipecoloxylidide [(*S*)-PPX]	Analysis of 2- and 8-hr urine samples showed that no metabolic racemization of ropivacaine, which consists of only the (*S*)-(–)-form, occurred in humans. Also, no (*R*)-(+)-enantiomers of PPX or 3'-hydroxyropivacaine were detected. The limit of detection of the assay was 2 ng/mL for the (*R*)-(+)-enantiomer of ropivacaine and 10 ng/mL for the (*R*)-(+)-enantiomers of the metabolites PPX and 3'-hydroxyropivacaine.	Arvidsson et al. (1994)
One rabbit (sex n.p.)	i.v. dose of ropivacaine hydrochloride (2 mg)	Determined metabolites in the plasma of rabbits. Metabolites found and their amounts in plasma at 60 min were: Ropivacaine [ROP] (~100 ng/mL) Pipecoloxylidide [(*S*)-PPX](~10 ng/mL) 3'-Hydroxyropivacaine [(*S*)-3'-ROPOH] (~5 ng/mL)	Blood was collected for 60 min post administration. Plasma concentrations of PPX rose exponentially and reached a plateau of about 10 ng/mL from 15 to 60 min after i.v. administration. Plasma concentrations of 3'-hydroxyropivacaine rose exponentially and reached a plateau of about 3 ng/mL from 15 to 60 min after i.v. administration. No 4'-hydroxyropivacaine was detected.	Reif et al. (1998)

Table F-1. Metabolism Studies of Ropivacaine in Humans and Experimental Animals (Continued)

Subjects	Dose	Compounds Determined	Remarks	Reference
In Vitro Studies				
Human Hepatic Microsomes	Incubation of microsomes (200 µg of protein) with ropivacaine (0.1 mM) with addition of antibodies for isozyme determination	Pipecoloxylidide [(*S*)-PPX] 4'-Hydroxyropivacaine [(*S*)-4'-ROPOH] 3'-Hydroxyropivacaine [(*S*)-3'-ROPOH]	Metabolism by human hepatic P450 enzymes resulted in the formation of PPX, 4'-hydroxyropivacaine, and 3'-hydroxyropivacaine. The major metabolite detected was PPX. The human P450 isozymes CYP3A4 and CYP1A2 were the major metabolizing enzymes.	Oda et al. (1995)
Rat Hepatic Microsomes	0.1 mM ropivacaine incubated with 200 µg of protein; addition of antibodies for isozyme determination	Pipecoloxylidide [(*S*)-PPX] 4'-Hydroxyropivacaine [(*S*)-4'-ROPOH] 3'-Hydroxyropivacaine [(*S*)-3'-ROPOH]	Metabolism by rat hepatic P450 enzymes resulted in the formation of PPX, 4'-hydroxyropivacaine, and 3'-hydroxyropivacaine. The major metabolite detected was PPX. The rat P450 isozymes CYP2C11, CYP3A2, CYP2D1, and CYP1A2 were the major metabolizing enzymes.	Oda et al. (1995)
Human Liver Microsomes from 2 Indilsvidua	Incubation with ropivacaine (0.5-1.0 mM) for 30 min	The determined compounds along with V_{max} in pmol/mg/min were: Pipecoloxylidide [(*S*)-PPX] (1847) 4'-Hydroxyopivacaine [(*S*)-4'-ROPOH] (105) 3'-Hydroxyropivacaine [(*S*)-3'-ROPOH] (46) 2'-Hydroxymethylropivacaine [(*S*)-□-ROP] (9)	The formation of 3'-hydroxyropivacaine was mediated by CYP1A and the formation of 4'-hydroxyropivacaine, 2'-hydroxymethylropivacaine, and PPX is catalyzed by CYP3A and possibly CYP2C.	Ekström and Gunnarsson (1996)

Table F-1. Metabolism Studies of Ropivacaine in Humans and Experimental Animals (Continued)

Subjects	Dose	Compounds Determined	Remarks	Reference
Human Liver Microsomes from 12 Patients	Incubation with ropivacaine (0.5-1.0 mM) in the presence of NADPH and various inhibitors for 30 min	Determined the effect of enzyme inhibition on the metabolism of ropivacaine *in vitro*. Compounds detected after incubationn with ropivacaine were: Pipecoloxylidide [(*S*)-PPX] 4'-Hydroxyropivacaine [(*S*)-4'-ROPOH] 2'-Hydroxymethylropivacaine [(S)-□-ROPOH]	When cimetidine, a nonspecific P450 inhibitor, was added at high concentrations (1 mM) to the incubation medium, there was a 40-50% inhibition of 4-hydroxyropivacaine, 2-hydroxymethylropivacaine, and PPX formation. Addition of high concentrations of sulfaphenazole (100 mM) to the medium resulted in a 20-27% inhibition in the formation of 4'-hydroxyropivacaine, 2'-hydroxymethyl-ropivacaine, and pipecoloxylidide. Quinidine or diethyl dithiocarbamate had no effect on metabolite formation when added to the incubation medium. The addition of □-naphthoflavone (2 and 10 □M) or furafylline (5 and 50 □M) almost completely inhibited 3'-hydroxyropivacaine formation, but did not affect the formation of 4'-hydroxyropivacaine, 2'-hydroxymethyl-ropivacaine, and pipecoloxylidide. It is possible that drug interactions at the enzyme level may occur with other drugs that are preferentially metabolized by CYP1A. However, because of ropivacaine's low affinity for CYP3A and the abundance of the enzyme in the liver, the risk of drug interactions is not expected.	Ekström and Gunnarsson (1996)
cDNA expressed P450 proteins	Incubation with ropivacaine (1 mM) for 2 hr	Determined the effect of enzyme inhibition on the metabolism of ropivacaine *in vitro*. Compounds determined in the medium were: 3'-Hydroxyropivacaine [(S)-3'-ROPOH] 2'-Hydroxymethylropivacaine [(S)-□-ROPOH] Pipecolylidide [PPX]	Cells expressing CYP1A2 catalyzed only the formation of 3'-hydroxyropivacaine and cells expressing CYP3A4 formed 2'-hydroxymethylropivacaine and PPX. Very small amounts of PPX were formed by cells expressing CYP1A1 and CYP2D6 and very small amounts of 3'-hydroxyropivacaine were formed by cells expressing CYP2D6.	Ekström and Gunnarsson (1996)

Table F-1. Metabolism Studies of Ropivacaine in Humans and Experimental Animals (Continued)

Subjects	Dose	Compounds Determined	Remarks	Reference
5 Cloned Human Cytosolic Sulfotransferases (STs)	Metabolites of ropivacaine in a concentration range between 0.125 and 200 µM	3'-Hydroxypipecoloxylidide [(*S*)-3'-PPXOH] 3'-Hydroxyropivacaine [(*S*)-3'-ROPOH] 4'-Hydroxyropivacaine [(*S*)-4'-ROPOH] 2'-Hydroxymethylropivacaine [(*S*)-2'-MeOH-ROP] 2'-Carboxyropivacaine [(*S*)-PIP-AMBA]	The five known metabolites of ropivacaine were used as substrates for 5 STs: P-PST-1, M-PST, EST, ST1B2, and DHEA-ST. None of the metabolites was sulfonated by DHEA-ST. All of the metabolites except 2'-hydroxymethylropivacaine and 2'-carboxyropivacaine were sulfated. The metabolite most extensively sulfated was 3'-hydroxypipecoloxylidide. The most efficient enzyme at sulfating the ropivacaine metabolites was M-PST. Since M-PST and ST1B2 are present in the circulation, there may be some sulfation of the hydroxylated metabolites occurring throughout the entire body (Heroux and Roth, 1988; Wang et al., 1998).	Falany et al. (1999)

Abbreviations: F = female(s); hr = hour(s); i.v. = intravenous; M = male(s); min = minute(s)

Table F-2. Pharmacokinetics Studies of Ropivacaine in Humans and Experimental Animals

Subjects	Dose	Remarks	Reference
9 Healthy Human Males (24-43 yrs)	Simultaneous administration of ropivacaine hydrochloride epidurally (150 mg, 7.5 mg/mL) for 5 min and $^{2}H_{3}$-ropivacaine hydrochloride i.v. (40 mg; 0.25 mg/mL) for 30 min	Absorption after epidural administration was biphasic, characterized by an initial rapid phase of $t_{1/2,ka1}$ = 14 min followed by a slower phase of $t_{1/2,ka2}$ = 4.2 hr. The mean terminal half-life of ropivacine was 4.3 hr. Arterial blood plasma concentrations increased faster than venous plasma concentrations by as much as 50% after both i.v and epidural administration. The estimated rate of clearance from the blood was 320 mL/min after i.v administration. The elimination $t_{1/2}$ from venous plasma was 1.7 hr after i.v administration and 4.2 hr after epidural administration of ropivacaine. The mean peak venous (1.09 ± 0.30 mg/L) and arterial (1.58 ± 0.34 mg/L) plasma concentrations of ropivacaine after epidural block were higher than those seen in venous (0.82 ± 0.19) and arterial (1.27 ± 0.17) plasma after i.v. administration. The time to peak venous concentrations of ropivacaine was the same after both routes, but arterial concentrations peaked sooner after epidural block (20 min) than with i.v. (30 min). The analgesic effect was correlated with the slower absorption-phase half-life; the greater the half-life, the longer the analgesic effect. It was suggested that monitoring of arterial blood concentrations of ropivacaine rather than venous concentrations would be better for predicting toxic reactions.	Emanuelsson et al. (1997)
6 Healthy Males	i.v. infusion of ^{14}C-labeled ropivacaine hydrochloride monohydrate (50 mg) in the forearm for 15 min	The urinary excretion of radioactivity from ^{14}C-labeled ropivacaine in humans (86% of dose in 96 hr) is higher than that in rats (~41%) and dogs (63%), but similar to urinary excretion in pregnant rabbits (92%). The mean elimination half-life was 5.4 ± 2.9 hr (range: 3.2-10.4 hr) for total radioactivity and 2.0 ± 0.3 hr (range: 1.5-2.4 hr) for ropivacaine. The longer half-life of total radioactivity was due to the presence of metabolites. The mean peak plasma level of ropivacaine was 5.5 ± 2.4 µM (range was 2.5-8.2 µM). at 0-5 min. after infusion. The total plasma clearance of ropivacaine was 397 ± 127 mL/min.	Halldin et al. (1996)
24 Healthy Human Males (age: 20-42 yr)	Continuous 21-hr epidural infusion with 0.1, 0.2, or 0.3% ropivacaine (total dose of 220, 440, or 660 mg)	The plasma concentrations of ropivacaine increased continuously (linearly) throughout the 21-hour infusion period, reaching a plateau (designated C_{5-10}) at approximately 5 to 10 hr after the start of infusion. The mean C_{5-10} plateau concentrations were 0.29, 0.56, and 0.92 mg/L for the 220, 440, and 660 mg dose groups, respectively. The peak plasma concentrations were 0.39, 0.88, and 1.19 mg/L, respectively, observed at the termination of infusion at 21 hr. The mean half-life in plasma, measured after infusion termination, of ropivacaine was 3.0, 3.2, and 2.6 hr, respectively. The rate of clearance, independent of the infusion rate, was estimated to be approximately 430 mL/min. These values were all for total plasma concentration, including protein-bound fractions. A mean 6.1% of the plasma concentration of ropivacaine was actually free unbound.	Emanuelsson et al. (1995)

Table F-2. Pharmacokinetics Studies of Ropivacaine in Humans and Experimental Animals (Continued)

Subjects	Dose	Remarks	Reference
12 Subjects (6M. 6F)	i.v. infusion with ropivacaine (40 mg) for 20 min; Some doses were supplemented with ketoconazole (400 mg) and fluvoxamine (100 mg)	Three groups received ropivacaine alone or ropivacaine along with fluvoxamine and ketoconazole, inhibitors of CYP1A2 and CYP3A4, respectively. Mean clearance of ropivacaine alone was 354 ± 110 mL/min and the elimination half-life was 1.9 ± 0.5 hr. The mean plasma concentration of ropivacaine immediately after administration was 1.23 ± 0.21 mg/L. The mean percent of ropivacaine unbound in plasma was 5.2 ± 1.3%. The extent of protein binding was not significantly altered by the enzyme inhibitors. Fluvoxamine caused a significant increase in the mean elimination half-life (3.6 ± 1.1 hr) and plasma concentration at the end of infusion (1.46 ± 0.24 mg/L), but caused a decrease in the clearance of ropivacaine from plasma (112 ± 27 mL/min). Less than 15% of the total clearance was mediated by enzymatic pathways other than CYP1A2 and CYP3A4, and CYP1A2 is the most important isozyme involved in the metabolism of ropivacaine.	Arlander (1998)
77 Male Adults (undergoing hernia repair surgery)	Injection of 0.2, 0.5, and 0.75% ropivacaine (0.25 mL/kg) to the anterior iliac spine for 2 min	Based on peripheral venous samples, the concentration of ropivacaine peaked in plasma at 30 min after administration in the 0.2 and 0.5% groups and 45 min post-administration in the 0.75% group. Mean peak concentrations of ropivacaine in plasma were 0.3 ± 0.15 µg/mL, 0.75 ± 0.45 µg/mL, and 1.57 ± 0.82 µg/mL in the 0.2%, 0.5%, and 0.75% group, respectively. These plasma concentrations were far below concentrations that cause mild central nervous system toxicity in humans (1-2 mg/L) (Scott et al., 1989)	Wulf et al. (1999)
20 Women (undergoing hysterectomies for benign diseases)	Epidural administration of ropivacaine (2.5 mg/mL) for 24 hr (2 groups of ten women were infused with either 10 mg/hr or 20 mg/hr); initial test dose of 7.5 mg ropivacaine	Total plasma concentrations of ropivacaine increased 36% in the 10 mg/hr group (from 0.39 ± 0.16 to 0.53 ± 0.22 mg/L) and 38% in the 20 mg/hr dose group (from 0.64 ± 0.23 to 0.88 ± 0.24 mg/L) during the last 12 hr of infusion. No plateau concentration of ropivacaine in plasma was seen during infusion. The mean total doses were 290 mg in the 10 mg/hr groups and 511 mg in the 20 mg/hr dose group. The apparent terminal half-life was 2.4 ± 0.9 hr in the 10 mg/hr group and 2.7 ± 0.9 hr in the 20 mg/hr group. The mean unbound ropivacaine in plasma between 8-24 hr of infusion was ~0.018 mg/L in the 10 mg/hr dose group and 0.034 mg/L in the 20 mg/hr group, far below the estimated human CNS toxic concentration of 0.6 mg/L. The plasma unbound fraction of ropivacaine 7 and 8.7 hours into infusion in the 10 and 20 mg/hr groups was 5.6 ± 1.2% and 5.2 ± 1.4%, respectively. Plasma protein binding had increased significantly (~2%) by the end of infusion as a result of increased plasma protein content. Total plasma clearance (418 ± 138 mL/min) was independent of the dose. Unchanged ropivacaine recovered in 24-hr urine samples was 0.4 to 3.0% of the dose. Unbound plasma concentrations of ropivacaine are stable, in contrast to increasing total concentration during epidural administration. Analgesia was more effective in the 20 mg/hr dose group.	Erichsen et al. (1996)

Table F-2. Pharmacokinetics Studies of Ropivacaine in Humans and Experimental Animals (Continued)

Subjects	Dose	Remarks	Reference
15 Patients undergoing elective orthopedic surgery	Epidural dose of 20 mL containing 0.5, 0.75, or 1% ropivacaine in three groups of five patients each	The maximum concentrations of ropivacaine in serum in the 0.5, 0.75, and 1% ropivacaine groups were 0.53, 1.07, and 1.53 □g/mL, respectively. The mean clearance of ropivacaine was 0.35 and 0.34 L/kg/hr in the 0.5 and 0.75% dose groups, respectively, and 0.52 L/kg/hr in the 1% ropivacaine dose group. This clearance is similar to that reported in Lee et al. (in press?) of 43.2 ± 9.6 L/hr. There was no significant difference in the clearance or ropivacaine in the three groups. The mean residence times (MRT) of ropivacaine in the body in the 0.5, 0.75, and 1% groups were 9.92, 7.53, and 4.47 hours, respectively. The MRT was significantly different in the 0.5% group. The apparent decrease in MRT with increasing concentration was due to the longer t_{max} and lower clearance in two individuals in the 0.5% dose groups. The bioavailability (AUC) was 5.65, 8.22, and 6.20, respectively.	Katz et al. (1990)
11 Patients (3F, 8M; undergoing elective orthopedic hip or knee surgery)	Post-operative epidural infusion with ropivacaine (2 mg/mL) at a rate of 6 mL/hr for a mean duration of 108 ± 22 min; doses: 690-1559 mg	Plasma concentrations increased with time and no plateau was observed during infusion; however, the unbound ropivacaine in plasma reached a plateau or began to decline during the infusion period. Peak maximum plasma concentrations of ropivacaine were between 1.1 and 5.2 mg/L. The highest concentration of ropivacaine in plasma and greatest bioavailability was seen in a patient with a history of liver cirrhosis. The median $t_{1/2}$ was determined to be 5.1 hr (range: 2.0-13.3 hr). The maximum unbound fraction of ropivacaine in plasma was 0.015-0.150 mg/L, but decreased to 0.013-0.109 mg/L by the end of the infusion period. The unbound fraction varied between 1.2 and 14.1%. The median concentrations of □$_1$-acid glycoprotein increased from 20 □mol/L before surgery to 35 □mol/L 74-83 hr after the start of post-operative infusion of ropivacaine, very similar to what was seen by Erichsen et al. (1996).	Scott et al. (1997)
1 21-mo-old Girl (undergoing brachytherapy[a type of radiotherapy])	epidural infusion with 0.5 or 0.75% ropivacaine for 72 hr	Plasma concentrations of ropivacaine were 1.83 □g/mL 22 hr after the initiation of infusion and 1.54 □g/mL 48 hr later. Analgesia was the same with ropivacaine and bupivacaine, but ropivacaine (0.5%) caused less motor block than bupivacaine (0.5%), which is in agreement with Brockway et al. (1991). The mean dose of ropivacaine rose from 1.40 mg/kg/hr after 24 hr of infusion to 3.86 mg/kg/hr after 78 hr. Over time, it required more anesthetic to achieve the required degree of motor block. The reduction in plasma concentration of ropivacaine by the end of the treatment period was possibly due to increased metabolism as a result of preceding chemotherapy and enzyme induction.	Gustorff et al. (1999)
4 Rats (All Male; Strain n.p.)	i.v. or s.c. dose of 10 µmol/kg	Analysis of 30-min urine samples found no metabolic racemization of ropivacaine.	Arvidsson et al. (1994)

Table F-2. Pharmacokinetics Studies of Ropivacaine in Humans and Experimental Animals (Continued)

Subjects	Dose	Remarks	Reference
6 Adult Rhesus Monkeys	i.v. administration of ropivacaine (1 mg/kg) for 1 min; 2 wk later epidural administration of 0.5% ropivacaine (10 mg; two 1-mL doses for 60 sec administered 5 min apart)	After i.v. administration, the mean $t_{1/2\beta}$ was 2.07 hr, the mean residence time was 1.632 hr, and the mean clearance was 0.71 L/kg/hr. Serum concentrations-time profiles following i.v. administration were bi-exponential. The mean bioavailability following epidural administration was 0.950. After epidural administration, approximately 50% of the ropivacaine dose was absorbed during the initial rapid absorption phase (mean $t_{1/2\beta}$ = 0.06 hr) and 50% was absorbed during the subsequent slower absorption phase ($t_{1/2\beta}$ = 6.48 hr). In one monkey, serum concentrations of ropivacaine after i.v. administration were 2-3 μg/mL immediately after dosing and 0.1 μg/mL 2.0 hr later. After epidural administration in the same monkey, serum concentrations were slightly more than 1 μg/mL 10-15 min after administration and 0.1 μg/mL 5 hr later. Ropivacaine's larger steady state volume of distribution when compared to bupivacaine and the fact that the two have similar serum protein binding suggest that there may be more extensive tissue binding of ropivacaine. Higher clearance rates for the local anesthetics are seen in lower primates due to their higher basal heart rate (200 beats/min); however, distribution and elimination half-lives in primates correlate well with those of humans (Densonet al., 1981). Following a single i.v. dose of ropivacaine in humans, the median elimination $t_{1/2}$ was 111 min compared to the median of 118 min in the present study. While systemic uptake of ropivacaine from the epidural space may be faster than that of bupivacaine (especially in the initial rapid phase), the duration of sensory blockade and the peak plasma concetrations are similar in the two agents. The intersubject variability was thought to be due to individual epidural fat content or regional blood flow changes.	Katz et al. (1993)
Four Dogs (3M, 1F; Strain n.p.)	Given a rectal dose of 20 μmol/kg ropivacaine, an s.c dose of 10 μmol/kg, or i.v. infusion of 10 μmol/kg	Analysis of a 24-hr urine samples found no metabolic racemization of ropivacaine, which consists of only the (–)-(S)-form. The limit of determination of the assay was 0.2% for the (+)-(R)-enantiomer of ropivacaine.	Arvidsson et al. (1994)
2 Sheep (1 pregnant and 1 nonpregnant)	i.v infusion of 6 μmol/kg ropiva-caine over 15 min	Analysis of 30-min urine samples found no metabolic racemization of ropivacaine.	Arvidsson et al. (1994)

Abbreviations: F = female(s); bw = body weight; hr = hour(s); i.v. = intravenous; M = male(s); min = minute(s); mo = month(s); yr = year(s)

APPENDIX G

Some Amide Local Anesthetics and Their Metabolites in Order by CAS Registry Number (CASRN)

Some Amide Local Anesthetics and Their Metabolites in Order By CAS Registry Number (CASRN)

Parent (shaded) or Metabolite Code[a]	Metabolite	Hill Formula	CASRN	Chem. Abstr. References & References Used	Metabolite of
4′-PRIOH	*p*-Hydroxyprilocaine; 4-Hydroxyprilocaine	$C_{13}H_{21}N_2O_2$	Not identified	Hjelm et al. (1972)	Prilocaine
3′,4′-oxy-MEP	1-Methylpipecolo-3′,4′-dihydro-3′,4′-epoxy-2′,6′-xylidide; 1-Methylpipecolo-3′,4′-dihydro-3′,4′-oxy-2′,6′-xylidide	$C_{15}H_{22}N_2O_2$	Not identified	Meffin and Thomas (1973)	Mepivacaine
(S)-PIP-AMBA	"(*S*)-2-Carboxyropivacaine;" 3-Methyl-2-[(1-propylpiperidine-2-carbonyl)amino]benzoic acid; (2*S*)-*N*-[(2-Carboxy)-6-methylphenyl]-1-propyl-2-piperidinecarboxamide **[Falany et al. (1999) conducted *in vitro* sulfation of synthesized known and suspected ropivacaine metabolites. Not derived as a metabolite. Not found in references cited.]**	$C_{17}H_{24}N_2O_4$	Not identified	Falany et al. (1999)	Ropivacaine **(conjectural)**
N-MEPOH	1-Methylpipecolo-*N*-hydroxy-2′,6′-xylidide; *N*-Hydroxymepivacaine **[Authors suggested possible rearrangement of the N-hydroxy group to the 4′-position. CAS did not index the abstract for this compound.]**	$C_{15}H_{22}N_2O_2$	Not identified	Meffin and Thomas (1973)	Mepivacaine
LID•HCl	Lidocaine hydrochloride	$C_{14}H_{23}ClN_2O$	73-78-9	929	Lidocaine salt (parent)
AABA	□-Aminobutyric acid; 2-Aminobutanoic acid; AABA; (✂)-□-Aminobutyric acid; *DL*-2-Aminobutyric acid; Butyrine; *DL*-Ethylglycine; Homoalanine	$C_4H_9NO_2$	80-60-4 (Replaced by 2835-81-6)	1269	Etidocaine **(conjectural)**
$C_6H_3Me_2NO_2$	1,3-Dimethyl-2-nitrobenzene; 2-Nitro-*m*-xylene; 2,6-Dimethylnitrobenzene; 2-Nitro-1,3-dimethylbenzene; 2-Nitro-1,3-xylene **[Possible metabolite, but no evidence (Kammerer and Schmitz (1986).]**	$C_8H_9NO_2$	81-20-9	190 Kammerer & Schmitz (1986)	Lidocaine
XYL	2,6-Xylidine; 2,6-Dimethylaniline	$C_8H_{11}N$	87-62-7	[24 with CASRN linked to metabolism] Thomas et al. (1996), Morgan et al. (1977b) (etidocaine); Keenaghan & Boyes (1972) (lidocaine)	Bupivacaine **(conjectural)**, Etidocaine, Lidocaine

Some Amide Local Anesthetics and Their Metabolites in Order By CAS Registry Number (CASRN)

Parent (shaded) or Metabolite Code[a]	Metabolite	Hill Formula	CASRN	Chem. Abstr. References & References Used	Metabolite of
MES	Mesidine; Mesitylamine; 2-Aminomesitylene; 2,4,6-Trimethylaniline; 2,4,6-Trimethylbenzeneamine; 1-Amino-2,4,6-trimethylbenzene; 2,4,6-Trimethylphenylamine	$C_9H_{13}N$	88-05-1	593	Trimecaine?
TOL	*o*-Toluidine; 2-Methylaniline; 2-Methylbenzeneamine; *o*-Tolylamine; 1-Amino-2-methylbenzene [Potential metabolites, including hydroxylamine and nitroso derivatives, and their CASRNs are listed in the EMICBACK records for Gupta et al. (1987, 1989).]	C_7H_9N	95-53-4	4739	Prilocaine
MEP	Mepivacaine; (−)-Mepivacaine; *DL*-Mepivacaine; Carbocaine; 1-Methyl-2′,6′-pipecoloxylidide; *N*-(2,6-Dimethylphenyl)-1-methyl-2-piperidinecarboxamide	$C_{15}H_{22}N_2O$	96-88-8	547	Mepivacaine (parent)
PrCHO	Butyraldehyde; Butanal **[A probable metabolite of a proposed metabolite (Bouché & Lhoest, 1976). No link was found between this compound and bupivacaine in Chem. Abstr.]**	C_4H_8O	123-72-8	7765 Bouché & Lhoest (1976)	Bupivacaine
LID	Lidocaine; Xylocaine; Lignocaine; 2-(Diethylamino)-2′,6′-acetoxylidide; □-Diethylamino-2,6-acetoxylidide	$C_{14}H_{22}N_2O$	137-58-6	5176	Lidocaine (parent)
PIP	Pipecolic acid; *DL*-Pipecolic acid; (□)-Pipecolic acid; □-Pipecolinic acid; (*RS*)-2-Piperidinecarboxylic acid; Piperolinic acid; Homoproline; 2-Carboxypiperidine; etc.	$C_6H_{11}NO_2$	535-75-1	518 Goehl et al. (1973)	Bupivacaine
4′-MEPOH	4′-Hydroxymepivacaine; *N*-(4-Hydroxy-2,6-dimethylphenyl)-1-methyl-2-piperidinecarboxamide; 4′-Hydroxy-1-methyl-2′,6′-pipecoloxylidide; 1-Methylpipecolo-4′-hydroxy-2′,6′-xylidide	$C_{15}H_{22}N_2O_2$	616-66-0	4 Meffin & Thomas (1973) Meffin et al. (1973a)	Mepivacaine
TRI	Trimecaine; Mesdicain; Mesidicaine; Diethylglycinemesidide; 2-(Diethylamino)-*N*-(2,4,6-trimethylphenyl)acetamide; .omega.-Diethylaminoacetylaminomesitylene; 2-(Diethylamino)-2′,4′,6′-trimethylacetanilide; *N*-(Diethylaminoacetyl)-2,4,6-trimethylaniline	$C_{15}H_{24}N_2O$	616-68-2	229	Trimecaine parent
EG	*N*-Ethylglycine; (Ethylamino)acetic acid	$C_4H_9NO_2$	627-01-0	47	Lidocaine

Some Amide Local Anesthetics and Their Metabolites in Order By CAS Registry Number (CASRN)

Parent (shaded) or Metabolite Code[a]	Metabolite	Hill Formula	CASRN	Chem. Abstr. References & References Used	Metabolite of
PRI	Prilocaine; *DL*-(±)-Prilocaine; Citanest; *N*-(2-Methylphenyl)-2-(propylamino)propanamide; *o*-Methyl-2-propylaminopropionanilide; 2-Methyl-α-propylaminopropionanilide; α-Propylamino-2-methylpropionanilide	$C_{13}H_{20}N_2O$	721-50-6	391	Prilocaine (parent)
TRI•HCl	Trimecaine hydrochloride	$C_{15}H_{25}ClN_2O$	1027-14-1	37	Trimecaine salt (parent)
DEG	*N*,*N*-Diethylglycine; (Diethylamino)acetic acid	$C_6H_{13}NO_2$	1606-01-5	63 Nelson et al. (1977)	Lidocaine
MEP•HCl	Mepivacaine hydrochloride; Carbocaine hydrochloride; Scandonest	$C_{15}H_{22}N_2O•ClH$	1722-62-9	107	Mepivacaine salt (parent)
PRI•HCl	Prilocaine hydrochloride; Xylonest	$C_{13}H_{21}ClN_2O$	1786-81-8	75	Prilocaine salt (parent)
TRI01	Monoethylglycylmesidide; *N*-(Ethylaminoacetyl)mesidine; 2-(Ethylamino)-*N*-(2,4,6-trimethylphenyl)acetamide; (*N*-Ethylglycyl)mesidine	$C_{13}H_{20}N_2O$	2105-31-9	5	Trimecaine
BUP	Bupivacaine; (±)-Bupivacaine; Marcaine; *DL*-Bupivacaine; 1-Butyl-*N*-(2,6-dimethylphenyl)-2-piperidinecarboxamide; 1-Butyl-2′,6′-pipecoloxylidide	$C_{18}H_{28}N_2O$	2180-92-9 (replaced by 38396-39-3 ca. 1991)	1128	Bupivacaine (parent)
PYR•HCl	Pyrrocaine hydrochloride	$C_{14}H_{21}ClN_2O$	2210-64-2	4	Pyrrocaine salt (parent)
PYR	Pyrrocaine; Dynacaine; Endocaine; *N*-(2,6-Dimethylphenyl)-1-pyrrolidineacetamide; 1-Pyrrolidineaceto-2′,6′-xylidide	$C_{14}H_{20}N_2O$	2210-77-7	13	Pyrrocaine (parent)
AABA	α-Aminobutyric acid; 2-Aminobutanoic acid; AABA; (±)-α-Aminobutyric acid; *DL*-2-Aminobutyric acid; Butyrine; *DL*-Ethylglycine; Homoalanine	$C_4H_9NO_2$	2835-81-6 (Replaced CASRN 80-60-4)	601	Etidocaine **(conjectural)**

Some Amide Local Anesthetics and Their Metabolites in Order By CAS Registry Number (CASRN)

Parent (shaded) or Metabolite Code[a]	Metabolite	Hill Formula	CASRN	Chem. Abstr. References & References Used	Metabolite of
6-TOLOH	*o*-Hydroxytoluidine; 6-Hydroxy-*o*-toluidine; 2-Amino-3-methylphenol; 3-Methyl-2-aminophenol; 2-Amino-*m*-cresol; 6-Hydroxy-2-methylaniline	C_7H_9NO	2835-97-4	44 Hjelm et al. (1972)	Prilocaine
4-TOLOH	*p*-Hydroxytoluidine; 4-Hydroxy-*o*-toluidine; 4-Amino-3-methylphenol; 4-Amino-*m*-cresol; 4-Hydroxy-2-methylaniline	C_7H_9NO	2835-99-6	326 Hjelm et al. (1972)	Prilocaine
LID-N-Ox	Lidocaine *N*-oxide; 2-(Diethyloxidoamino)-*N*-(2,6-dimethylphenyl)acetamide; 2-(Diethylamino)-*N*-(2,6-dimethylphenyl)acetamide N^2-oxide; 2-(Diethylamino)-2′,6′-xylidide **[Rat liver microsomes supplemented with NADPH metabolized lidocaine to the *N*-oxide (Patterson et al., 1986). No other studies were identified that found this compound as a lidocaine metabolite.]**	$C_{14}H_{22}N_2O_2$	2903-45-9	7 Patterson et al. (1986)	Lidocaine *in vitro*
N-XYLOH	*N*-Hydroxy-2,6-xylidine; 2,6-Dimethylphenylhydroxylamine	$C_{14}H_{22}N_2O_2$	3096-63-7	0 [See Nelson et al. (1977, 1978).]	Lidocaine
4-XYLOH	4-Hydroxy-2,6-xylidine; 4-Amino-3,5-dimethylphenol; 4-Amino-3,5-xylenol; 4-Amino-3,5-dimethylphenol; 4-Hydroxy-2,6-dimethylaniline	$C_8H_{11}NO$	3096-70-6	75 Thomas et al. (1996), Morgan et al. (1977b) (etidocaine); Tam et al. (1987) (lidocaine)	Etidocaine, Lidocaine
AMBA	2-Amino-3-methylbenzoic acid; 2-Amino-*m*-toluic acid; 3-Methyl-2-aminobenzoic acid; 3-Methylanthranilic acid	$C_8H_9NO_2$	4389-45-1	141 Kammerer & Schmitz (1986)	Lidocaine
LID•HCl•H₂O	Lidocaine hydrochloride monohydrate	$C_{14}H_{25}ClN_2O_2$	6108-05-0	6	Lidocaine salt (parent)
MEGX	MEGX; Monoethylglycinexylidide; Monoethylglycylxylidide; *N*-(2,6-Dimethylphenyl)-2-(ethylamino)acetamide; 2-(Ethylamino)-2′,6′-acetoxylidide; *N*-(*N*-Ethylglycyl)-2,6-xylidide; EGX; L 86; Deethyllidocaine; *N*,*N*-Ethylglycinexylidide; □-Ethylamino-2′,6′-dimethylacetanilide	$C_{12}H_{18}N_2O$	7728-40-7	209 Keenaghan & Boyes (1972)	Lidocaine
N-PrALA	*N*-*n*-Propylalanine; *N*-Propyl-*L*-alanine	$C_6H_{13}NO_2$	13013-28-0	3 Geddes (1965, 1967)	Prilocaine

Some Amide Local Anesthetics and Their Metabolites in Order By CAS Registry Number (CASRN)

Parent (shaded) or Metabolite Code[a]	Metabolite	Hill Formula	CASRN	Chem. Abstr. References & References Used	Metabolite of
BUP•HCl	Bupivacaine hydrochloride	$C_{18}H_{29}ClN_2O$	14252-80-3	40 Irestadt et al. (1976)	Bupivacaine salt (parent)
(+)-PRI	*L*-(+)-Prilocaine; (+)-Prilocaine; (*S*)-Prilocaine; (2*S*)-*N*-(2-Methylphenyl)-2-(propylamino)propanamide; *L*-(+)-2-(Propylamino)-*o*-propionotoluidide	$C_{13}H_{20}N_2O$	14289-31-7	20	Prilocaine (stereoisomer, parent)
(-)-PRI	*D*-(-)-Prilocaine; (-)-Prilocaine; (*R*)-Prilocaine; (2*R*)-*N*-(2-Methylphenyl)-2-(propylamino)propanamide; *D*-(-)-2-(Propylamino)-*o*-propionotoluidide	$C_{13}H_{20}N_2O$	14289-32-8	21	Prilocaine (stereoisomer, parent)
PPX	2′,6′-Pipecoloxylidide [racemic]; 2′,6′-Pipecolylxylidide; PPX; *N*-Desbutylbupivacaine; Mono-*N*-demethylmepivacaine; *N*-(2,6-Dimethylphenyl)-2-piperidinecarboxamide	$C_{14}H_{20}N_2O$	15883-20-2	45 Goehl et al. (1973) (bupivacaine); Hansson et al. (1965) (mepivacaine) (Frequently indexed as a ropivacaine metabolite when (S)-PPX [27262-40-4] is meant.)	Bupivacaine, Mepivacaine
BUP•HCl	Bupivacaine hydrochloride	$C_{18}H_{29}ClN_2O$	18010-40-7	144	Bupivacaine salt (parent)
GX	Glycine xylidide; Glycyl xylidide; *N*-Glycyl-2,6-xylidine; GX; 2-Amino-2′,6′-acetoxylidide; □-Amino-2,6-dimethylacetanilide; 2-Amino-2′,6′-dimethylacetanilide	$C_{10}H_{14}N_2O$	18865-38-8	106 Keenaghan & Boyes (1972)	Lidocaine
$C_6H_3Me_2NO$	1,3-Dimethyl-2-nitrosobenzene; 2-Nitroso-*m*-xylene; 2,6-Dimethylnitrosobenzene **[Possible metabolite, but no evidence (Kammerer and Schmitz (1986).]**	C_8H_9NO	19519-71-2	18 Kammerer & Schmitz (1986)	Lidocaine
LID•H_2SO_4	Lidocaine sulfate	$C_{14}H_{24}N_2O_5$	24847-67-4	3	Lidocaine salt (parent)

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Parent (shaded) or Metabolite Code[a]	Metabolite	Hill Formula	CASRN	Chem. Abstr. References & References Used	Metabolite of
(S)-PPX	(*S*)-2′,6′-Pipecoloxylidide; (*S*)-Desbutylbupivacaine; (+)-2′,6′-Pipecoloxylidide; (2*S*)-*N*-(2,6-Dimethylphenyl)-2-piperidinecarboxamide	$C_{14}H_{20}N_2O$	27262-40-4	20 Fawcett et al. (1999) (bupivacaine); Arlander et al. (1998), Arvidsson et al. (1995) (ropivacaine)	Bupivacaine, (*S*)-(-)
(R)-PPX	(*R*)-2′,6′-Pipecoloxylidide; (*R*)-Desbutylbupivacaine; (-)-2′,6′-Pipecoloxylidide	$C_{14}H_{20}N_2O$	27262-43-7	10 Fawcett et al. (1999) (bupivacaine); Arvidsson et al. (1995) (ropivacaine)	Bupivacaine, (*R*)-(+)- (27262-45-9); Ropivacaine **(very minor)**
(R+)-BUP	(+)-Bupivacaine; (*R*)-(+)-Bupivacaine; (*R*)-Bupivacaine; *D*-(+)-Bupivacaine; *d*-Bupivacaine	$C_{18}H_{29}ClN_2O$	27262-45-9	90	Bupivacaine (stereoisomer, parent)
(S-)-BUP	(-)-Bupivacaine; (*S*)-(-)-Bupivacaine; (*S*)-Bupivacaine; *L*-(-)-Bupivacaine; Levobupivacaine	$C_{18}H_{29}ClN_2O$	27262-47-1	114	Bupivacaine (stereoisomer, parent)
IMZ05	N^1-Ethyl-2-methyl-N^3-(2,6-dimethylphenyl)-4-imidazolidinone; 3-(2,6-Dimethylphenyl)-1-ethyl-2-methyl-4-imidazolidinone; 1-Ethyl-2-methyl-3-(2,6-xylyl)-4-imidazolidinone **[Probable source MEGX plus acetaldehyde source (e.g., ethanol) *in vivo* (established in Rhesus monkeys) or MEGX plus acetaldehyde in urine or acetaldehyde contaminant in solvents. Might also arise through intramolecular condensation of lidocaine (Breck and Trager, 1971; Nelson et al., 1973; Carrier et al., 1993)].**	$C_{14}H_{20}N_2O$	32845-42-4	3 Breck & Trager (1971) Nelson et al. (1977) Carrier et al. (1993)	Lidocaine
3′-LIDOH	3-Hydroxylidocaine; 2-(Diethylamino)-*N*-(3-hydroxy-2,6-dimethylphenyl)acetamide	$C_{14}H_{22}N_2O_2$	34604-55-2	46 Keenaghan & Boyes (1972)	Lidocaine
3′-MEGXOH	3-Hydroxy-*N*-(*N*-ethylglycyl)-2,6-xylidine; 2-(Ethylamino)-*N*-(3-hydroxy-2,6-dimethylphenyl)acetamide; 3′-Hydroxy-MEGX	$C_{12}H_{18}N_2O_2$	34604-56-3	20 Tam et al. (1987)	Lidocaine
ETI	Etidocaine; (±)-*N*-(2,6-Dimethylphenyl)-2-(ethylpropylamino)butanamide; 2-(*N*-Ethylpropylamino)-2′,6′-butyroxylidide	$C_{17}H_{28}N_2O$	36637-18-0	226	Etidocaine (parent)

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Parent (shaded) or Metabolite Code[a]	Metabolite	Hill Formula	CASRN	Chem. Abstr. References & References Used	Metabolite of
ETI▨HCl	Etidocaine hydrochloride; Duranest hydrochloride	$C_{17}H_{29}ClN_2O$	36637-19-1 (Replaced 52300-99-9)	43	Etidocaine salt (parent)
3′-MEPOH	3′-Hydroxymepivacaine; *N*-(3-Hydroxy-2,6-dimethylphenyl)-1-methyl-2-piperidinecarboxamide; 3′-Hydroxy-1-methyl-2′,6′-pipecoloxylidide; 1-Methylpipecolo-3′-hydroxy-2′,6′-xylidide **[Major mepivacaine metabolite in horses (Harkins, 1999)]**	$C_{15}H_{22}N_2O_2$	37055-90-6	4 Harkins (1999) Meffin & Thomas (1973) Meffin et al. (1973a)	Mepivacaine
BUP	Bupivacaine; (✂)-Bupivacaine; Marcaine; *DL*-Bupivacaine; 1-Butyl-*N*-(2,6-dimethylphenyl)-2-piperidinecarboxamide; 1-Butyl-2′,6′-pipecoloxylidide	$C_{18}H_{28}N_2O$	38396-39-3	517	Bupivacaine parent
4′-LIDOH	4-Hydroxylidocaine; 2-(Diethylamino)-*N*-(4-hydroxy-2,6-dimethylphenyl)acetamide	$C_{14}H_{22}N_2O_2$	39942-41-1	8 Keenaghan & Boyes (1972)	Lidocaine
6-oxo-PPX	*N*-(2,6-Dimethylphenyl)-6-oxo-2-pyridinecarboxamide; 6-Oxopipecolo-2′,6′-xylidide; 6-Oxopipecolo-2′,6′-xylide	$C_{14}H_{18}N_2O_2$	43063-88-3	1 Meffin et al. (1973b)	Mepivacaine
6-oxo-MEP	*N*-(2,6-Dimethylphenyl)-1-methyl-6-oxo-1-piperidinecarboxamide; 1-Methyl-6-oxo-2′,6′-pipecoloxylidide; 1-Methyl-6-oxopipecolo-2′,6′-xylidide	$C_{15}H_{20}N_2O_2$	43063-89-4	1 Meffin et al. (1973b)	Mepivacaine
	N-(2,6-Dimethylphenyl)-1-(hydroxymethyl)-6-oxo-2-pyridinecarboxamide; 1-Hydroxymethyl-6-oxo-2′,6′-pipecoloxylidide **[Examination of the original article (Meffin et al., 1973) provided no evidence for this compound. Apparently, the CASRN assignment was an indexing mistake for the abstract Chem. Abstr. 80:10211.]**	$C_{15}H_{20}N_2O_3$	43063-90-7	1 [Chemical Abstracts Service attributed to Meffin et al. (1973b).]	Mepivacaine ? **(indexing error)**
6-oxo-4/5-MEPOH	*N*-(2,6-Dimethylphenyl)hydroxy-1-methyl-6-oxo-2-piperidinecarboxamide; Hydroxy-1-methyl-6-oxo-2′,6′-pipecoloxylidide; Hydroxy-1-methyl-6-oxopipecolo-2′,6′-xylidide **[The author presumed a hydroxy group was on position 4 or 5 of the 6-oxo-2-piperidinecarboxamide ring.]**	$C_{15}H_{20}N_2O_3$	50306-98-4	1 Meffin et al. (1973b)	Mepivacaine
IMZ07	3-(2,6-Dimethylphenyl)-1-ethyl-4-imidazolidinone **[Possible formation from MEGX and endogenous or contaminant formaldehyde (Nelson et al., 1973).]**	$C_{13}H_{18}N_2O$	51044-98-5	1 Nelson et al. (1973)	Lidocaine

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Parent (shaded) or Metabolite Code[a]	Metabolite	Hill Formula	CASRN	Chem. Abstr. References & References Used	Metabolite of
3´-BUPOH	3´-Hydroxybupivacaine; 1-Butyl-*N*-(3-hydroxy-2,6-dimethylphenyl)-2-piperidinecarboxamide; 1-Butyl-3´-hydroxypipecolo-2,6´-xylidide	$C_{18}H_{28}N_2O_2$	51989-46-9	10 Dennhardt & Konder al. (1980)	Bupivacaine
4´-BUPOH	4´-Hydroxybupivacaine; 1-Butyl-*N*-(4-hydroxy-2,6-dimethylphenyl)-2-piperidinecarboxamide	$C_{18}H_{28}N_2O_2$	51989-47-0	13 Dennhardt & Konder (1980)	Bupivacaine
4´-PPXOH	4´-Hydroxy-2´,6´-pipecoloxylidide [racemic]; *N*-(4-Hydroxy-2,6-dimethylphenyl)-2-piperidinecarboxamide; 4´-Hydroxydesbutylbupivacaine	$C_{14}H_{20}N_2O_2$	51989-48-1	2 Falany et al. (1999) Goehl et al. (1973)	Bupivacaine
ETI•HCl	Etidocaine hydrochloride; Duranest hydrochloride	$C_{17}H_{29}ClN_2O$	52300-99-9 (See preferred 36637-19-1)	4	Etidocaine salt (parent)
	N-Hydroxy-MEGX; .omega.-(Ethylamino)-2,6-dimethylphenylacetohydroxamic acid; *N*-(2,6-Dimethylphenyl)-2-(ethylamino)-*N*-hydroxyacetamide **[Synthesized by Nelson et al. (1977) as a potential metabolite, but did not match any metabolites.]**	$C_{12}H_{18}N_2O_2$	52662-14-3	2 Nelson et al. (1974, 1977)	Lidocaine **(not found)**
	N-Hydroxylidocaine **[Synthesized by Nelson et al. (1977, 1978) as a potential metabolite, but did not match any metabolites.]**	$C_{14}H_{22}N_2O_2$	52662-13-2	3 Nelson et al. (1974, 1977, 1978)	Lidocaine **(not found)**
BUP•H_2CO_3	Bupivacaine carbonate; Bupiv-Carb	$C_{18}H_{28}N_2O•2CH_2O_3$	55750-21-5	3	Bupivacaine salt (parent)
LID•H_2CO_3	Lidocaine carbonate	$C_{14}H_{22}N_2O•2CH_2O_3$	56934-02-2	4	Lidocaine salt (parent)
ABX	2-Amino-2´-butyroxylidide; *N*-(2,6-Dimethylphenyl)-2-aminobutanamide	$C_{12}H_{18}N_2O$	59359-46-5	15 Thomas et al. (1996)	Etidocaine
EtABX	2-*N*-Ethylamino-2´-butyroxylidide; N-(2,6-Dimethylphenyl)-2-(ethylamino)butanamide	C14H22N2O	59359-47-6	3 Thomas et al. (1996)	Etidocaine

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Parent (shaded) or Metabolite Code[a]	Metabolite	Hill Formula	CASRN	Chem. Abstr. References & References Used	Metabolite of
PrABX	2-N-Propylamino-2´-butyroxylidide; N-(2,6-Dimethylphenyl)-2-(propylamino)butanamide	C15H24N2O	59359-48-7	3 Thomas et al. (1996)	Etidocaine
IMZ04	3-(2,6-Dimethylphenyl)-5-ethyl-2-methyl-4-imidazolidinone	C14H20N2O	59359-49-8	1 Thomas et al. (1976)	Etidocaine
b-BUPOH	N-(2,6-Dimethylphenyl)-1-(2-hydroxybutyl)-2-piperidinecarboxamide	C18H28N2O2	64013-17-8	1 Bouché & Lhoest (1976)	Bupivacaine
IMZ01	3-(2,6-Dimethylphenyl)-5-ethyl-2,4-imidazolidinedione	C13H16N2O2	64226-24-0 [113800-53-6 (R)-] [113800-58-1 (S)-]	1 Morgan et al. (1977c)	Etidocaine
IMZ03	1-(2,6-Dimethylphenyl)-2,4-diethyl-2-imidazolin-5-one; 3-(2,6-Dimethylphenyl)-2,5-diethyl-3,5-dihydro-4H-imidazol-4-one	C15H20N2O	64226-25-1	1 Morgan et al. (1977c)	Etidocaine
IMZ02	1-(2,6-Dimethylphenyl)-2-methyl-4-ethyl-2-imidazolin-5-one; 3-(2,6-Dimethylphenyl)-5-ethyl-3,5-dihydro-2-methyl-4H-imidazol-4-one	C14H18N2O	64429-46-5	1 Morgan et al. (1977c)	Etidocaine
4´-MEGXOH	p-Hydroxy-(-ethylamino-2,6-dimethylacetanilide; 2-(Ethylamino)-N-(4-hydroxy-2,6-dimethylphenyl)acetamide; 4´-Hydroxy-MEGX	C12H18N2O2	64585-10-0	5 Tam et al. (1987)	Lidocaine
-LIDOH	"Hydroxymethyllidocaine;" 2-(Diethylamino)-*N*-[2-(hydroxymethyl)-6-methylphenyl]acetamide	$C_{14}H_{22}N_2O_2$	64585-18-8	12 Tanaka et al. (1994) Carrier et al. (1993)	Lidocaine
BUPOH	Hydroxybupivacaine; 1-Butyl-*N*-(2,6-dimethylphenyl)hydroxy-2-piperidinecarboxamide [unspecified attachment for hydroxyl group]	$C_{18}H_{28}N_2O_2$	67800-43-5	1 Dennhardt et al. (1978a)	Bupivacaine

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Parent (shaded) or Metabolite Code[a]	Metabolite	Hill Formula	CASRN	Chem. Abstr. References & References Used	Metabolite of
N-Bu-PIPamide	*N*-Butylpipecolyl-2-amide; 1-Butyl-2-piperidinecarboxamide; *N*-Butylpiperidine-2-carboxylic acid amide **[Mentioned in Dennhardt et al. (1978a), Dennhardt and Konder (1980), and Dennhardt (1981) as "unexpected and unexplained." Formation of this compound would appear to require cleavage by hydrogenolysis of the C-N bond between the *m*-xylene and amino moieties of 2,6-xylidine.]**	$C_{10}H_{20}N_2O$	67810-45-1	1 Dennhardt & Konder (1980)	Bupivacaine
4′-ABXOH	2-Amino-*N*-(4-hydroxy-2,6-xylyl)butyramide; 2-Amino-*N*-(4-hydroxy-2,6-dimethylphenyl)butanamide	$C_{12}H_{18}N_2O_2$	69754-69-4	1 Vine et al. (1978)	Etidocaine
3′-EtABXOH	*N*-(3-Hydroxy-2,6-dimethylphenyl)-2-(ethylamino)butanamide; *N*-(2,6-Dimethyl-3-hydroxyphenyl)-2-(ethylamino)butanamide; 2-(Ethylamino)-*N*-(3-hydroxy-2,6-dimethylphenyl)butanamide (ditto all with "butyramide" instead of "butanamide")	$C_{14}H_{22}N_2O_2$	69754-70-7	1 Vine et al. (1978)	Etidocaine
4′-PrABXOH	*N*-(4-Hydroxy-2,6-dimethylphenyl)-2-(propylamino)butanamide; *N*-(2,6-Dimethyl-4-hydroxyphenyl)-2-propylaminobutyramide	$C_{15}H_{24}N_2O_2$	69754-71-8	1 Vine et al. (1978)	Etidocaine
4′-ETIOH	4-Hydroxyetidocaine; *N*-(2,6-Dimethyl-4-hydroxyphenyl)-2-(*N*,*N*-ethylpropylamino)butyramide; 2-(Ethylpropylamino)-*N*-(4-hydroxy-2,6-dimethylphenyl)butanamide	$C_{17}H_{28}N_2O_2$	69754-72-9	1 Vine et al. (1978)	Etidocaine
3′-ABXOH	2-Amino-*N*-(3-hydroxy-2,6-xylyl)butyramide; 2-Amino-*N*-(3-hydroxy-2,6-dimethylphenyl)butanamide	$C_{12}H_{18}N_2O_2$	69754-73-0	1 Vine et al. (1978)	Etidocaine
4′-EtABXOH	*N*-(4-Hydroxy-2,6-dimethylphenyl)-2-(ethylamino)butanamide; *N*-(2,6-Dimethyl-4-hydroxyphenyl)-2-(ethylamino)butanamide; 2-(Ethylamino)-*N*-(4-hydroxy-2,6-dimethylphenyl)butanamide (ditto all with "butyramide" instead of "butanamide")	$C_{14}H_{22}N_2O_2$	69754-74-1	1 Vine et al. (1978)	Etidocaine
3′-PrABXOH	*N*-(3-Hydroxy-2,6-dimethylphenyl)-2-(propylamino)butanamide; *N*-(2,6-Dimethyl-3-hydroxyphenyl)-2-(propylamino)butanamide (ditto all with "butyramide" instead of "butanamide")	$C_{15}H_{24}N_2O_2$	69754-75-2	1 Vine et al. (1978)	Etidocaine

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Parent (shaded) or Metabolite Code[a]	Metabolite	Hill Formula	CASRN	Chem. Abstr. References & References Used	Metabolite of
3´-ETIOH	3-Hydroxyetidocaine; *N*-(2,6-Dimethyl-3-hydroxyphenyl)-2-(*N*,*N*-ethylpropylamino)butyramide; 2-(Ethylpropylamino)-*N*-(3-hydroxy-2,6-dimethylphenyl)butanamide	$C_{17}H_{28}N_2O_2$	69754-76-3	1 Vine et al. (1978)	Etidocaine
(S)-ROP	Ropivacaine; (*S*)-(-)-Ropivacaine; (-)-Ropivacaine; (-)-LEA; (2*S*)-*N*-(2,6-Dimethylphenyl)-1-propyl-2-piperidinecarboxamide; (-)-1-Propyl-2´,6´-pipecoloxylidide	$C_{17}H_{26}N_2O$	84057-95-4	162	Ropivacaine (parent)
TRI02	*N*-Glycylmesidide; *N*-(Aminoacetyl)mesidine; 2-Amino-*N*-(2,4,6-trimethylphenyl)acetamide	$C_{11}H_{16}N_2O$	92885-79-5	4	Trimecaine
(S)-ROP•HCl	Ropivacaine hydrochloride	$C_{17}H_{27}ClN_2O$	98717-15-8	11	Ropivacaine salt (parent)
3-XYLOH	3-Hydroxy-2,6-xylidine; 3-Amino-2,4-dimethylphenol	$C_8H_{11}NO$	100445-96-3	4 Coutts et al. (1987)	Lidocaine
4´-GXOH	4-Hydroxy-*N*-glycyl-2,6-xylidine; 2-Amino-*N*-(4-hydroxy-2,6-dimethylphenyl)acetamide; 4´-Hydroxy-GX	$C_{10}H_{14}N_2O_2$	108966-35-4	2 Tam et al. (1987)	Lidocaine
3´-GXOH	3-Hydroxy-*N*-glycyl-2,6-xylidine; 2-Amino-*N*-(3-hydroxy-2,6-dimethylphenyl)acetamide; 3´-Hydroxy-GX	$C_{10}H_{14}N_2O_2$	112606-87-8	1 Coutts et al. (1987)	Lidocaine
(S)-ROP•HCl•H2O	Ropivacaine hydrochloride monohydrate	$C_{17}H_{29}ClN_2O_2$	132112-35-7	6	Ropivacaine salt (parent)
IMZ06	3-(2,6-Dimethylphenyl)-1,2-diethyl-4-imidazolidinone **[Formed by lidocaine oxidation by biomimetic systems (Carrier et al., 1993).]**	$C_{15}H_{22}N_2O$	152361-30-3	1 Carrier et al. (1993)	Lidocaine
(S)-3´-ROPOH	(-)-3´-Hydroxyropivacaine; 3´-Hydroxyropivacaine; (*S*)-3´-Hydroxy-1-propyl-2´,6´-pipecoloxylidide; (2*S*)-*N*-(3-Hydroxy-2,6-dimethylphenyl)-1-propyl-2-piperidinecarboxamide	$C_{17}H_{26}N_2O_2$	163589-30-8	8 Halldin et al. (1996)	Ropivacaine
(S)-4´-ROPOH	(-)-4´-Hydroxyropivacaine; (*S*)-4´-Hydroxy-1-propyl-2´,6´-pipecoloxylidide; (2*S*)-*N*-(4-Hydroxy-2,6-dimethylphenyl)-1-propyl-2-piperidinecarboxamide	$C_{17}H_{26}N_2O_2$	163589-31-9	5 Halldin et al. (1996)	Ropivacaine

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Parent (shaded) or Metabolite Code[a]	Metabolite	Hill Formula	CASRN	Chem. Abstr. References & References Used	Metabolite of
(S)-β-ROPOH	(2*S*)-*N*-[2-(Hydroxymethyl)-6-methylphenyl]-1-propyl-2-piperidinecarboxamide; 2-OH-methyl-ropivacaine [*sic*, Ekstrom & Gunnarsson (1996)]	$C_{17}H_{26}N_2O_2$	182703-01-1	2 Halldin et al. (1996)	Ropivacaine
(S)-3′-PPXOH	(*S*)-3′-Hydroxy-2′,6′-pipecoloxylidide; (*S*)-3′-Hydroxy-2′,6′-PPX; (2*S*)-*N*-(3-Hydroxy-2,6-dimethylphenyl)-2-piperidinecarboxamide **[Has not been reported as a bupivacaine metabolite.]**	$C_{14}H_{20}N_2O_2$	182878-70-2	2 Halldin et al. (1996) Arvidsson et al. (1999)	Ropivacaine
(S)-4′-BUPOH	(2*S*)-4′-Hydroxybupivacaine; (2*S*)-1-Butyl-*N*-(4-hydroxy-2,6-dimethylphenyl)-2-piperidinecarboxamide	$C_{18}H_{28}N_2O_2$	220604-01-3	1 Fawcett et al. (1999)	Bupivacaine
(S)-3′-BUPOH	(2*S*)-3′-Hydroxybupivacaine; (2*S*)-1-Butyl-*N*-(3-hydroxy-2,6-dimethylphenyl)-2-piperidinecarboxamide	$C_{18}H_{28}N_2O_2$	220604-03-5	1 Fawcett et al. (1999)	Bupivacaine (stereoisomer)
(R)-4′-BUPOH	(2*R*)-4′-Hydroxybupivacaine; (2*R*)-1-Butyl-*N*-(4-hydroxy-2,6-dimethylphenyl)-2-piperidinecarboxamide	$C_{18}H_{28}N_2O_2$	220604-05-7	1 Fawcett et al. (1999)	Bupivacaine
(R)-3′-BUPOH	(2*R*)-3′-Hydroxybupivacaine; (2*R*)-1-Butyl-*N*-(3-hydroxy-2,6-dimethylphenyl)-2-piperidinecarboxamide	$C_{18}H_{28}N_2O_2$	220604-08-0	1 Fawcett et al. (1999)	Bupivacaine (stereoisomer)
(S)-4′-PPXOH	(*S*)-4′-Hydroxy-2′,6′-pipecoloxylidide; (*S*)-4′-Hydroxy-2′,6′-PPX; (2*S*)-*N*-(4-Hydroxy-2,6-dimethylphenyl)-2-piperidinecarboxamide **[Proposed ropivacaine metabolite, but no evidence for this compound as a human metabolite.]**	$C_{14}H_{20}N_2O_2$	243989-47-1	1 Arvidsson et al. (1999)	Ropivacaine **(proposed)**
3′-PPXOH	3′-Hydroxy-2′,6′-pipecoloxylidide [racemic]; *N*-(3-Hydroxy-2,6-dimethylphenyl)-2-piperidinecarboxamide; 3′-Hydroxydesbutylbupivacaine	$C_{14}H_{20}N_2O_2$	247061-17-2	1 Arvidsson et al. (1999)	Bupivacaine

[a] (R)- and (S)- prefixes indicate specific optically active enantiomers.
Primes on numbers in codes indicate that ring hydroxylation is on the xylidine or toluidine moiety. Primes are not used on codes for xylidine and toluidine.
Numbers without primes in codes indicate that substitution is not on the xylidine or toluidine moiety (usually on the pipecolyl moiety).
The lower-case Greek letter beta in a code indicates that hydroxylation is on the C-2 of the butyl moiety.
The lower-case Greek letter alpha in a code indicates that hydroxylation is on a xylidine methyl group.

APPENDIX H

Compound Codes in Alphabetical Order

APPENDIX H. Compound Codes in Alphabetical Order

Code[a]	Compound Names	CASRN	Metabolite of
AABA	□-Aminobutyric acid; 2-Aminobutanoic acid; AABA; (±)-□-Aminobutyric acid; *DL*-Aminobutyric acid; Butyrine; *DL*-Ethylglycine; Homoalanine	2835-81-6 (replaced 80-60-4)	Etidocaine (conjectural)
ABX	2-Amino-2′-butyroxylidide; *N*-(2,6-Dimethylphenyl)-2-aminobutanamide	59359-46-5	Etidocaine
3′-ABXOH	2-Amino-*N*-(3-hydroxy-2,6-xylyl)butyramide; 2-Amino-*N*-(3-hydroxy-2,6-dimethylphenyl)butanamide	69754-73-0	Etidocaine
4′-ABXOH	2-Amino-*N*-(4-hydroxy-2,6-xylyl)butyramide; 2-Amino-*N*-(4-hydroxy-2,6-dimethylphenyl)butanamide	69754-69-4	Etidocaine
AMBA	2-Amino-3-methylbenzoic acid; 2-Amino-*m*-toluic acid; 3-Methyl-2-aminobenzoic acid; 3-Methylanthranilic acid	4389-45-1	Lidocaine
BUP	Bupivacaine; (±)-Bupivacaine; Marcaine; *DL*-Bupivacaine; 1-Butyl-*N*-(2,6-dimethylphenyl)-2-piperidinecarboxamide; 1-Butyl-2′,6′-pipecoloxylidide	38396-39-3 (replaced 2180-92-9)	Bupivacaine (parent)
(R+)-BUP	(+)-Bupivacaine; (*R*)-(+)-Bupivacaine; (*R*)-Bupivacaine; *D*-(+)-Bupivacaine; *d*-Bupivacaine	27262-45-9	Bupivacaine (stereoisomer, parent)
(S-)-BUP	(-)-Bupivacaine; (*S*)-(-)-Bupivacaine; (*S*)-Bupivacaine; *L*-(-)-Bupivacaine; Levobupivacaine	27262-47-1	Bupivacaine (stereoisomer, parent)
BUP·HCl	Bupivacaine hydrochloride	18010-40-7 (replaced 14252-80-3)	Bupivacaine salt (parent)
BUP·H_2CO_3	Bupivacaine carbonate; Bupiv-Carb	55750-21-5	Bupivacaine salt (parent)
N-Bu-PIPamide	*N*-Butylpipecolyl-2-amide; 1-Butyl-2-piperidinecarboxamide; *N*-Butylpiperidine-2-carboxylic acid amide	67810-45-1	Bupivacaine
BUPOH	Hydroxybupivacaine; 1-Butyl-*N*-(2,6-dimethylphenyl)hydroxy-2-piperidinecarboxamide [unspecified attachment for hydroxyl group]	67800-43-5	Bupivacaine
3′-BUPOH	3′-Hydroxybupivacaine; 1-Butyl-*N*-(3-hydroxy-2,6-dimethylphenyl)-2-piperidinecarboxamide; 1-Butyl-3′-hydroxypipecolo-2,6′-xylidide	51989-46-9	Bupivacaine
(R)-3′-BUPOH	(2*R*)-3′-Hydroxybupivacaine; (2*R*)-1-Butyl-*N*-(3-hydroxy-2,6-dimethylphenyl)-2-piperidinecarboxamide	220604-08-0	Bupivacaine (stereoisomer)
(S)-3′-BUPOH	(2*S*)-3′-Hydroxybupivacaine; (2*S*)-1-Butyl-*N*-(3-hydroxy-2,6-dimethylphenyl)-2-piperidinecarboxamide	220604-03-5	Bupivacaine (stereoisomer)
4′-BUPOH	4′-Hydroxybupivacaine; 1-Butyl-*N*-(4-hydroxy-2,6-dimethylphenyl)-2-piperidinecarboxamide	51989-47-0	Bupivacaine
(R)-4′-BUPOH	(2*R*)-4′-Hydroxybupivacaine; (2*R*)-1-Butyl-*N*-(4-hydroxy-2,6-dimethylphenyl)-2-piperidinecarboxamide	220604-05-7	Bupivacaine
(S)-4′-BUPOH	(2*S*)-4′-Hydroxybupivacaine; (2*S*)-1-Butyl-*N*-(4-hydroxy-2,6-dimethylphenyl)-2-piperidinecarboxamide	220604-01-3	Bupivacaine
□-BUPOH	*N*-(2,6-Dimethylphenyl)-1-(2-hydroxybutyl)-2-piperidinecarboxamide	64013-17-8	Bupivacaine
$C_6H_3Me_2NO$	1,3-Dimethyl-2-nitrosobenzene; 2-Nitroso-*m*-xylene; 2,6-Dimethylnitrosobenzene	19519-71-2	Lidocaine (conjectural)
$C_6H_3Me_2NO_2$	1,3-Dimethyl-2-nitrobenzene; 2-Nitro-*m*-xylene; 2,6-Dimethylnitrobenzene; 2-Nitro-1,3-dimethylbenzene; 2-Nitro-1,3-xylene	81-20-9	Lidocaine (conjectural)
DEG	*N*,*N*-Diethylglycine; (Diethylamino)acetic acid	1606-01-5	Lidocaine
EG	*N*-Ethylglycine; (Ethylamino)acetic acid	627-01-0	Lidocaine
EtABX	2-*N*-Ethylamino-2′-butyroxylidide; *N*-(2,6-Dimethylphenyl)-2-(ethylamino)butanamide	59359-47-6	Etidocaine

Code[a]	Compound Names	CASRN	Metabolite of
3´-EtABXOH	*N*-(3-Hydroxy-2,6-dimethylphenyl)-2-(ethylamino)butanamide; *N*-(2,6-Dimethyl-3-hydroxyphenyl)-2-(ethylamino)butanamide; 2-(Ethylamino)-*N*-(3-hydroxy-2,6-dimethylphenyl)butanamide (ditto all with "butyramide" instead of "butanamide")	69754-70-7	Etidocaine
4´-EtABXOH	*N*-(4-Hydroxy-2,6-dimethylphenyl)-2-(ethylamino)butanamide; *N*-(2,6-Dimethyl-4-hydroxyphenyl)-2-(ethylamino)butanamide; 2-(Ethylamino)-*N*-(4-hydroxy-2,6-dimethylphenyl)butanamide (ditto all with "butyramide" instead of "butanamide")	69754-74-1	Etidocaine
ETI	Etidocaine; (±)-*N*-(2,6-Dimethylphenyl)-2-(ethylpropylamino)butanamide; 2-(*N*-Ethylpropylamino)-2´,6´-butyroxylidide	36637-18-0	Etidocaine (parent)
ETI·HCl	Etidocaine hydrochloride; Duranest hydrochloride	36637-19-1 (replaced 52300-99-9)	Etidocaine salt (parent)
3´-ETIOH	3-Hydroxyetidocaine; *N*-(2,6-Dimethyl-3-hydroxyphenyl)-2-(*N*,*N*-ethylpropylamino)butyramide; 2-(Ethylpropylamino)-*N*-(3-hydroxy-2,6-dimethylphenyl)butanamide	69754-76-3	Etidocaine
4´-ETIOH	4-Hydroxyetidocaine; *N*-(2,6-Dimethyl-4-hydroxyphenyl)-2-(*N*,*N*-ethylpropylamino)butyramide; 2-(Ethylpropylamino)-*N*-(4-hydroxy-2,6-dimethylphenyl)butanamide	69754-72-9	Etidocaine
GX	Glycine xylidide; Glycyl xylidide; *N*-Glycyl-2,6-xylidine; GX; 2-Amino-2´,6´-acetoxylidide; □-Amino-2,6-dimethylacetanilide; 2-Amino-2´,6´-dimethylacetanilide	18865-38-8	Lidocaine
3´-GXOH	3-Hydroxy-*N*-glycyl-2,6-xylidine; 2-Amino-*N*-(3-hydroxy-2,6-dimethylphenyl)acetamide; 3´-Hydroxy-GX	112606-87-8	Lidocaine
4´-GXOH	4-Hydroxy-*N*-glycyl-2,6-xylidine; 2-Amino-*N*-(4-hydroxy-2,6-dimethylphenyl)acetamide; 4´-Hydroxy-GX	108966-35-4	Lidocaine
IMZ01	3-(2,6-Dimethylphenyl)-5-ethyl-2,4-imidazolidinedione	64226-24-0	Etidocaine
IMZ02	1-(2,6-Dimethylphenyl)-2-methyl-4-ethyl-2-imidazolin-5-one; 3-(2,6-Dimethylphenyl)-5-ethyl-3,5-dihydro-2-methyl-4*H*-imidazol-4-one	64429-46-5	Etidocaine
IMZ03	1-(2,6-Dimethylphenyl)-2,4-diethyl-2-imidazolin-5-one; 3-(2,6-Dimethylphenyl)-2,5-diethyl-3,5-dihydro-4*H*-imidazol-4-one	64226-25-1	Etidocaine
IMZ04	3-(2,6-Dimethylphenyl)-5-ethyl-2-methyl-4-imidazolidinone	59359-49-8	Etidocaine
IMZ05	N^1-Ethyl-2-methyl-N^3-(2,6-dimethylphenyl)-4-imidazolidinone; 3-(2,6-Dimethylphenyl)-1-ethyl-2-methyl-4-imidazolidinone; 1-Ethyl-2-methyl-3-(2,6-xylyl)-4-imidazolidinone	32845-42-4	Lidocaine
IMZ06	3-(2,6-Dimethylphenyl)-1,2-diethyl-4-imidazolidinone	152361-30-3	Lidocaine
IMZ07	3-(2,6-Dimethylphenyl)-1-ethyl-4-imidazolidinone	51044-98-5	Lidocaine
LID	Lidocaine; Xylocaine; Lignocaine; 2-(Diethylamino)-2´,6´-acetoxylidide; □-Diethylamino-2,6-acetoxylidide	137-58-6	Lidocaine (parent)
LID·HCl	Lidocaine hydrochloride	73-78-9	Lidocaine salt (parent)
LID·HCl·H_2O	Lidocaine hydrochloride monohydrate	6108-05-0	Lidocaine salt (parent)
LID·H_2CO_3	Lidocaine carbonate	56934-02-2	Lidocaine salt (parent)
LID·H_2SO_4	Lidocaine sulfate	24847-67-4	Lidocaine salt (parent)
3´-LIDOH	3-Hydroxylidocaine; 2-(Diethylamino)-*N*-(3-hydroxy-2,6-dimethylphenyl)acetamide	34604-55-2	Lidocaine
4´-LIDOH	4-Hydroxylidocaine; 2-(Diethylamino)-*N*-(4-hydroxy-2,6-dimethylphenyl)acetamide	39942-41-1	Lidocaine
□-LIDOH	"Hydroxymethyllidocaine;" 2-(Diethylamino)-*N*-[2-(hydroxymethyl)-6-methylphenyl]acetamide	64585-18-8	Lidocaine
LID-N-Ox	Lidocaine *N*-oxide; 2-(Diethyloxidoamino)-*N*-(2,6-dimethylphenyl)acetamide; 2-(Diethylamino)-*N*-(2,6-dimethylphenyl)acetamide N^2-oxide; 2-(Diethylamino)-2´,6´-xylidide	2903-45-9	Lidocaine *in vitro*
MEGX	MEGX; Monoethylglycinexylidide; Monoethylglycylxylidide; *N*-(2,6-Dimethylphenyl)-2-(ethylamino)acetamide; 2-(Ethylamino)-2´,6´-acetoxylidide; *N*-(*N*-Ethylglycyl)-2,6-xylidide; EGX; L 86; Deethyllidocaine; *N*,*N*-Ethylglycinexylidide; □-Ethylamino-2´,6´-dimethylacetanilide	7728-40-7	Lidocaine

Code[a]	Compound Names	CASRN	Metabolite of
3′-MEGXOH	3-Hydroxy-*N*-(*N*-ethylglycyl)-2,6-xylidine; 2-(Ethylamino)-*N*-(3-hydroxy-2,6-dimethylphenyl)acetamide; 3′-Hydroxy-MEGX	34604-56-3	Lidocaine
4′-MEGXOH	*p*-Hydroxy-□-ethylamino-2,6-dimethylacetanilide; 2-(Ethylamino)-*N*-(4-hydroxy-2,6-dimethylphenyl)acetamide; 4′-Hydroxy-MEGX	64585-10-0	Lidocaine
MEP	Mepivacaine; (±)-Mepivacaine; *DL*-Mepivacaine; Carbocaine; 1-Methyl-2′,6′-pipecoloxylidide; *N*-(2,6-Dimethylphenyl)-1-methyl-2-piperidinecarboxamide	96-88-8	Mepivacaine (parent)
MEP·HCl	Mepivacaine hydrochloride; Carbocaine hydrochloride; Scandonest	1722-62-9	Mepivacaine salt (parent)
3′-MEPOH	3′-Hydroxymepivacaine; *N*-(3-Hydroxy-2,6-dimethylphenyl)-1-methyl-2-piperidinecarboxamide; 3′-Hydroxy-1-methyl-2′,6′-pipecoloxylidide; 1-Methylpipecolo-3′-hydroxy-2′,6′-xylidide	37055-90-6	Mepivacaine
4′-MEPOH	4′-Hydroxymepivacaine; *N*-(4-Hydroxy-2,6-dimethylphenyl)-1-methyl-2-piperidinecarboxamide; 4′-Hydroxy-1-methyl-2′,6′-pipecoloxylidide; 1-Methylpipecolo-4′-hydroxy-2′,6′-xylidide	616-66-0	Mepivacaine
N-MEPOH	1-Methylpipecolo-*N*-hydroxy-2′,6′-xylidide; *N*-Hydroxymepivacaine	Not identified	Mepivacaine
6-oxo-MEP	*N*-(2,6-Dimethylphenyl)-1-methyl-6-oxo-1-piperidinecarboxamide; 1-Methyl-6-oxo-2′,6′-pipecoloxylidide; 1-Methyl-6-oxopipecolo-2′,6′-xylidide	43063-89-4	Mepivacaine
6-oxo-4/5-MEPOH	*N*-(2,6-Dimethylphenyl)hydroxy-1-methyl-6-oxo-2-piperidinecarboxamide; Hydroxy-1-methyl-6-oxo-2′,6′-pipecoloxylidide; Hydroxy-1-methyl-6-oxopipecolo-2′,6′-xylidide	50306-98-4	Mepivacaine
6-oxo-PPX	*N*-(2,6-Dimethylphenyl)-6-oxo-2-pyridinecarboxamide; 6-Oxopipecolo-2′,6′-xylidide; 6-Oxopipecolo-2′,6′-xylide	43063-88-3	Mepivacaine
3′,4′-oxy-MEP	1-Methylpipecolo-3′,4′-dihydro-3′,4′-epoxy-2′,6′-xylidide; 1-Methylpipecolo-3′,4′-dihydro-3′,4′-oxy-2′,6′-xylidide	Not identified	Mepivacaine
PIP	Pipecolic acid; *DL*-Pipecolic acid; (±)-Pipecolic acid; □-Pipecolinic acid; (*RS*)-2-Piperidinecarboxylic acid; Piperolinic acid; Homoproline; 2-Carboxypiperidine; etc.	535-75-1	Bupivacaine
(S)-PIP-AMBA	"(*S*)-2-Carboxyropivacaine;" 3-Methyl-2-[(1-propylpiperidine-2-carbonyl)amino]benzoic acid; (2*S*)-*N*-[(2-Carboxy)-6-methylphenyl]-1-propyl-2-piperidinecarboxamide	Not identified	Ropivacaine (conjectural)
PPX	2′,6′-Pipecoloxylidide [racemic]; 2′,6′-Pipecolylxylidide; PPX; *N*-Desbutylbupivacaine; Mono-*N*-demethylmepivacaine; *N*-(2,6-Dimethylphenyl)-2-piperidinecarboxamide	15883-20-2	Bupivacaine, Mepivacaine, Ropivacaine
(R)-PPX	(*R*)-2′,6′-Pipecoloxylidide; (*R*)-Desbutylbupivacaine; (-)-2′,6′-Pipecoloxylidide	27262-43-7	Bupivacaine, (*R*)-(+)-, Ropivacaine (very minor)
(S)-PPX	(*S*)-2′,6′-Pipecoloxylidide; (*S*)-Desbutylbupivacaine; (+)-2′,6′-Pipecoloxylidide; (2*S*)-*N*-(2,6-Dimethylphenyl)-2-piperidinecarboxamide	27262-40-4	Bupivacaine, (*S*)-(-), Ropivacaine
3′-PPXOH	3′-Hydroxy-2′,6′-pipecoloxylidide [racemic]; *N*-(3-Hydroxy-2,6-dimethylphenyl)-2-piperidinecarboxamide; 3′-Hydroxydesbutylbupivacaine	247061-17-2	Bupivacaine
(S)-3′-PPXOH	(*S*)-3′-Hydroxy-2′,6′-pipecoloxylidide; (*S*)-3′-Hydroxy-2′,6′-PPX; (2*S*)-*N*-(3-Hydroxy-2,6-dimethylphenyl)-2-piperidinecarboxamide **[Has not been reported as a bupivacaine metabolite.]**	182878-70-2	Ropivacaine
4′-PPXOH	4′-Hydroxy-2′,6′-pipecoloxylidide [racemic]; *N*-(4-Hydroxy-2,6-dimethylphenyl)-2-piperidinecarboxamide; 4′-Hydroxydesbutylbupivacaine	51989-48-1	Bupivacaine
(S)-4′-PPXOH	(*S*)-4′-Hydroxy-2′,6′-pipecoloxylidide; (*S*)-4′-Hydroxy-2′,6′-PPX; (2*S*)-*N*-(4-Hydroxy-2,6-dimethylphenyl)-2-piperidinecarboxamide	243989-47-1	Ropivacaine (proposed)
PrABX	2-*N*-Propylamino-2′-butyroxylidide; *N*-(2,6-Dimethylphenyl)-2-(propylamino)butanamide	59359-48-7	Etidocaine
3′-PrABXOH	*N*-(3-Hydroxy-2,6-dimethylphenyl)-2-(propylamino)butanamide; *N*-(2,6-Dimethyl-3-hydroxyphenyl)-2-(propylamino)butanamide (ditto all with "butyramide" instead of "butanamide")	69754-75-2	Etidocaine
4′-PrABXOH	*N*-(4-Hydroxy-2,6-dimethylphenyl)-2-(propylamino)butanamide; *N*-(2,6-Dimethyl-4-hydroxyphenyl)-2-propylaminobutyramide	69754-71-8	Etidocaine
N-PrALA	*N*-*n*-Propylalanine; *N*-Propyl-*L*-alanine	13013-28-0	Prilocaine
PrCHO	Butyraldehyde; Butanal	123-72-8	Bupivacaine (conjectural)

Code[a]	Compound Names	CASRN	Metabolite of
PRI	Prilocaine; *DL*-(±)-Prilocaine; Citanest; *N*-(2-Methylphenyl)-2-(propylamino)propanamide; *o*-Methyl-2-propylaminopropionanilide; 2-Methyl-□-propylaminopropionanilide; □-Propylamino-2-methylpropionanilide	721-50-6	Prilocaine (parent)
(+)-PRI	*L*-(+)-Prilocaine; (+)-Prilocaine; (*S*)-Prilocaine; (2*S*)-*N*-(2-Methylphenyl)-2-(propylamino)propanamide; *L*-(+)-2-(Propylamino)-*o*-propionotoluidide	14289-31-7	Prilocaine (stereoisomer, parent)
(-)-PRI	*D*-(-)-Prilocaine; (-)-Prilocaine; (*R*)-Prilocaine; (2*R*)-*N*-(2-Methylphenyl)-2-(propylamino)propanamide; *D*-(-)-2-(Propylamino)-*o*-propionotoluidide	14289-32-8	Prilocaine (stereoisomer, parent)
PRI·HCl	Prilocaine hydrochloride; Xylonest	1786-81-8	Prilocaine salt (parent)
4´-PRIOH	*p*-Hydroxyprilocaine; 4-Hydroxyprilocaine	Not identified	Prilocaine
(S)-ROP	Ropivacaine; (*S*)-(-)-Ropivacaine; (-)-Ropivacaine; (-)-LEA; (2*S*)-*N*-(2,6-Dimethylphenyl)-1-propyl-2-piperidinecarboxamide; (-)-1-Propyl-2´,6´-pipecoloxylidide	84057-95-4	Ropivacaine (parent)
(S)-ROP·HCl	Ropivacaine hydrochloride	98717-15-8	Ropivacaine salt (parent)
(S)-ROP·HCl·H_2O	Ropivacaine hydrochloride monohydrate	132112-35-7	Ropivacaine salt (parent)
(S)-3´-ROPOH	(-)-3´-Hydroxyropivacaine; 3´-Hydroxyropivacaine; (*S*)-3´-Hydroxy-1-propyl-2´,6´-pipecoloxylidide; (2*S*)-*N*-(3-Hydroxy-2,6-dimethylphenyl)-1-propyl-2-piperidinecarboxamide	163589-30-8	Ropivacaine
(S)-4´-ROPOH	(-)-4´-Hydroxyropivacaine; (*S*)-4´-Hydroxy-1-propyl-2´,6´-pipecoloxylidide; (2*S*)-*N*-(4-Hydroxy-2,6-dimethylphenyl)-1-propyl-2-piperidinecarboxamide	163589-31-9	Ropivacaine
(S)-□-ROPOH	(2*S*)-*N*-[2-(Hydroxymethyl)-6-methylphenyl]-1-propyl-2-piperidinecarboxamide; 2-OH-methyl-ropivacaine [*sic*, Ekstrom & Gunnarsson (1996)]	182703-01-1	Ropivacaine
TOL	*o*-Toluidine; 2-Methylaniline; 2-Methylbenzeneamine; *o*-Tolylamine; 1-Amino-2-methylbenzene	95-53-4	Prilocaine
6-TOLOH	*o*-Hydroxytoluidine; ^-Hydroxy-*o*-toluidine; 2-Amino-3-methylphenol; 3-Methyl-2-aminophenol; 2-Amino-*m*-cresol; 6-Hydroxy-2-methylaniline	2835-97-4	Prilocaine
4-TOLOH	*p*-Hydroxytoluidine; 4-Hydroxy-*o*-toluidine; 4-Amino-3-methylphenol; 4-Amino-*m*-cresol	2835-99-6	Prilocaine
XYL	2,6-Xylidine; 2,6-Dimethylaniline	87-62-7	Bupivacaine (conjectural), Etidocaine, Lidocaine
3-XYLOH	3-Hydroxy-2,6-xylidine; 3-Amino-2,4-dimethylphenol	100445-96-3	Lidocaine
4-XYLOH	4-Hydroxy-2,6-xylidine; 4-Amino-3,5-dimethylphenol; 4-Amino-3,5-xylenol; 4-Amino-3,5-dimethylphenol; 4-Hydroxy-2,6-dimethylaniline	3096-70-6	Etidocaine, Lidocaine
N-XYLOH	*N*-Hydroxy-2,6-xylidine; 2,6-Dimethylphenylhydroxylamine	3096-63-7	Lidocaine

[a] (R)- and (S)- prefixes indicate specific optically active enantiomers.
Primes on numbers in codes indicate that ring hydroxylation is on the xylidine or toluidine moiety. Primes are not used on codes for hydroxyl derivatives of xylidine and toluidine.
Numbers without primes in codes indicate that substitution is not on the xylidine or toluidine moiety (usually on the pipecolyl moiety).
The lower-case Greek letter beta in a code indicates that hydroxylation is on the C-2 of the butyl moiety.
The lower-case Greek letter alpha in a code indicates that hydroxylation is on a xylidine methyl group.

APPENDIX I

Units and Abbreviations

APPENDIX I: Units and Abbreviations

°C = degrees Celsius

μg/L = microgram(s) per liter

μg/mL = microgram(s) per milliliter

μM = micromolar

μm = micrometer

ACh = acetylcholine

bw = body weight

CD_{50} = convulsive dose of 50% of subjects

CE = capillary electrophoresis (also called capillary isotachophoresis)

CK = creatine kinase

CNS = central nervous system

CVS = cardiovascular system

DOT = U.S. Department of Transportation

EC_{50} = effective dose (for a particular endpoint) elicited in 50% of subjects

EEG = electroencephalogram

EPA = U.S. Environmental Protection Agency

F = female(s)

FDA = Food and Drug Administration

FID = flame ionization detector

FPIA = fluorescence polarization immunoassay

g = gram(s)

g/mL = gram(s) per milliliter

GC = gas chromatography

HPLC = high performance liquid chromatography

hr = hour(s)

i.m. = intramuscular(ly)

i.p. = intraperitoneal(ly)

i.t. = intratracheal(ly)

i.v. = intravenous(ly)

kg = kilogram(s)

L = liter(s)

lb = pound(s)

LC = liquid chromatography

LC_{50} = lethal concentration for 50% of test animals

LD_{50} = lethal dose for 50% of test animals

LD_{LO} = lethal dose low—lowest dose (other than LD_{50}) of a substance given by any route other than inhalation reported to have caused death in humans or animals.

LLE = liquid-liquid extraction

LOD = limit of detection

LOQ = limit of quantitation

M = male(s) or molar

mg/kg = milligram(s) per kilogram

mg/kg/hr = milligram(s) per kilogram per hour

mg/kg/min = milligram(s) per kilogram per minute

mg/m^3 = milligram(s) per cubic meter

mg/mL = milligram(s) per milliliter

min = minute(s)

mL = milliliter(s)

mL/kg = milliliter(s) per kilogram

mM = millimolar

MMLLE = microporous membrane LLE

mmol = millimole(s)

mmol/kg = millimoles per kilogram

mo = month(s)

mol = mole(s)

mol. wt. = molecular weight

MS = mass spectrometry

MS/MS = tandem mass spectrometry

n = number

NA = not applicable

NPD = nitrogen-phosphorus detection

NIEHS = National Institute of Environmental Health Sciences

NK = natural killer

nm = nanometer(s)

n.p. = not provided

NTP = National Toxicology Program

ppm = parts per million

p.o. = peroral(ly), *per os*

s = second(s)

s.c. = subcutaneous(ly)

SIM = selected ion monitoring

SLM = supported liquid membrane (extraction)

SPE = solid-phase extraction

TD_{LO} = toxic dose low—lowest dose of a substance given by any route other than inhalation reported to have caused toxic effect in humans or carcinogenic, neoplastigenic, or teratogenic effect in humans or animals.

TLC = thin layer chromatography

TPA = 12-*O*-tetradecanoylphorbol-13-acetate

UV = ultraviolet

wk = week(s)

yr = year(s)

APPENDIX J

Analytical Determination of Amide Local Anesthetics

APPENDIX J: Analytical Determination of Amide Local Anesthetics

This summary of analytical methods to determine amide local anesthetics in biological matrices and pharmaceutical preparations aims to identify the analytes, separation and detection methods, the matrix, and the limits of detection (LOD) and quantitation (LOQ) when available. Occasionally, sensitivity values are given instead of LODs or LOQs. [Sensitivity refers to the lowest measurable concentration that is distinguishable from zero with 95% confidence.] This Appendix does not aim to be comprehensive; many of the data were extracted from database abstracts (usually equivalent to author abstracts). Sample preparation methods, although of great importance, have generally not been discussed in detail. Recent reviews and original papers were examined to give a snapshot of currently used techniques. Older reviews are mentioned to give historical context. Techniques that rarely appeared in recent references were not included in this summary.

When Heusler (1985) reviewed analytical methods to determine the amide local anesthetics and their metabolites in biological fluids and tissues and in pharmaceuticals, methods were usually based on separation by gas chromatography (GC). In the 1970s and 1980s, packed-column GC methods predominated for determining lidocaine and lidocaine metabolites monoethylglycinexylidide (MEGX) and glycinexylidide (GX) and bupivacaine, etidocaine, mepivacaine, and their common metabolite 2', 6'-pipecoloxylidide (PPX). Detection methods included mass spectrometry (MS) (1 reference), flame ionization detectors (FID) (14 references), and nitrogen (N)-FID (12 references). Sensitivities were at least 2.5 ng/mL, but were usually greater than 20 ng/mL. Four studies using capillary GC with detection by N-FID or MS with selected ion monitoring (SIM) were reviewed that had high sensitivity peak levels of no more than 100 ng/mL for lidocaine, MEGX, GX, and bupivacaine. The five high performance liquid chromatography (HPLC) studies reviewed used ultraviolet (UV) detection at 195, 200, or 205 nm. Since the mid-1980s capillary GC and HPLC have become more commonly used.

Bupivacaine

In their review of analytical methods for bupivacaine, Schieferecke et al. (1998) cited two thin layer chromatography (TLC) studies published in 1973 and 1977, seven GC studies published from 1971 to 1990, and nine HPLC studies published from 1971 to 1996. The authors stated that the most recent analytical methods to determine bupivacaine and its metabolites simultaneously have used HPLC combined with liquid-liquid extraction (LLE), solid-phase extraction (SPE), or column switching. HPLC following LLE has been used to determine bupivacaine and metabolites in human serum, plasma, and urine.

In recently published capillary GC/MS studies for determination of bupivacaine and metabolites, bupivacaine LODs reported were ~10 ng/mL blood (Watanabe et al., 1998), 0.5 ng/mL plasma (Shen et al., 1998), 40 ng/mL plasma or urine (Ohshima and Takayasu, 1999), and ~5 ng/mL urine (Zhang et al., 1998).

The LOQs for recent HPLC methods to determine bupivacaine in plasma usually range up to about 20 ng/mL. However, Dal Bo et al. (1999) reported an LOD of 0.015 ng/mL and an LOQ of 0.20 ng/mL for the determination of bupivacaine in plasma by HPLC-tandem mass spectrometry (MS/MS).

Capillary electrophoresis (CE) (also called capillary isotachophoresis) and HPLC with a chiral stationary phase are used to separate enantiomers of bupivacaine and its metabolites (e.g., Bressolle et al., 1996, and Fawcett et al., 1999). Several earlier studies describing methods for enantiomeric separation were cited by Arvidsson et al. (1994). Gu et al. (1998) reported an improved, semi-automated chiral HPLC/UV assay for enantiomeric selective measurements of bupivacaine and metabolites with an LOD for each bupivacaine enantiomer of 15 ng/mL. The method featured a one-step extraction for sample preparation and high throughput. Schieferecke et al. (1998) used SPE with separation by CE for simultaneous separation and determination of bupivacaine and three of its metabolites in rat urine. The limits of detection in micromolar concentrations were bupivacaine (0.22 [63 ng/mL]), PPX (0.22), 3'-hydroxybupivacaine (3'-BUPOH) (0.15), and 4'-hydroxybupivacaine (4'-BUPOH) (0.16).

Knight (1999) reviewed methods published in the past 5 years that use detection by electrogenerated chemiluminescence (ECL) in the determination of bupivacaine and numerous other drugs in pharmaceuticals.

Etidocaine

Packed-column GC methods for etidocaine determination in plasma and urine had method sensitivities of 20 to 100 ng/mL (Heusler, 1985).

Lofti et al. (1997; cited by Dal Bo et al., 1999) reported an HPLC/UV method that could determine etidocaine in human plasma with an LOQ of 10 ng/mL.

Lidocaine

Heusler (1985) reviewed packed-column GC and HPLC methods for the determination of lidocaine and its metabolites MEGX and GX in body fluids and tissues.

Rizk et al. (1997) cited 28 publications from 1980 to 1996 reporting on the determination of lidocaine or its hydrochloride in pharmaceutical preparations. Methods included second-derivative spectrophotometry (1), extraction of a cobalt thiocyanate complex (1), reaction with bromcresol green (1), HPLC with various mobile phases and columns (7), TLC (2), GC (7), potentiometry using ion-selective electrodes (6), and atomic absorption spectrometry (as metal derivatives) (4). (The new visible spectrophotometric methods reported by the authors involved conversion colored derivatives.) Green (1987) reviewed lidocaine determination by electrochemical immunoassays.

Sensitivities for the packed-column GC methods reviewed by Heusler (1985) ranged from 2.5 ng/mL for plasma to 500 ng/mL for tissue analysis. Recent publications of capillary GC/MS determinations have reported considerably lower LOQs. Ohshima and Takayasu (1999) reported LOQs of 50 ng/mL for lidocaine and 100 ng/mL for MEGX and LODs of 40 ng/mL and 80 ng/mL for lidocaine and MEGX, respectively, in human plasma and urine. Watanabe et al. (1998) reported a lidocaine LOD of about 50 ng/mL in human blood. A capillary GC/MS/MS method for analysis of biological samples had a lidocaine LOD of 0.25 ng/mL vs. 5 ng/mL for GC/FID (van Hout et al., 1999). Sample preparation by microporous membrane LLE (MMLLE) followed by capillary GC with nitrogen-phosphorus detection (NPD) allowed determination of lidocaine in plasma with an LOD of 1 ng/mL (Shen et al., 1998). Use of GC/NPD after SPE achieved a comparable LOD of 1 ng/mL plasma (Laroche et al., 1998). Parker et al. (1996) used GC/MS-SIM to determine 4-hydroxyxylidine (4-XYLOH), MEGX, 2,6-xylidine, and other lidocaine metabolites in human liver slice culture medium. The LOQ was 1 μM (about 230 ng/mL for lidocaine) for all compounds.

Five publications that reported the determination of lidocaine and its metabolites in plasma or serum by reversed-phase HPLC with UV detection were reviewed by Heusler (1985). Method sensitivities ranged from 20 to 10,000 ng/mL. Wong (1989) reviewed advances in liquid chromatography for therapeutic monitoring of lidocaine and other drugs, usually in plasma or serum, as practiced in the United States.

O'Neal and Poklis (1996) reported LODs of 5 ng/mL plasma for MEGX and GX and 100 ng/mL for lidocaine using HPLC/UV. An HPLC/UV method with sample preparation by SPE had an LOQ of 20 ng/mL for lidocaine determination in 0.5 mL plasma samples and an LOD of 10 ng/mL (Kang et al., 1999). Solid-phase microextraction (SPME) preceding HPLC/UV allowed lidocaine determination in human urine with an LOD of 25 ng/mL, whereas the LOD using capillary GC/FID was 5 ng/mL (Koster et al., 1998). Parissi-Poulou and Panderi (1999) used SPE plus HPLC/UV-Vis to determine lidocaine hydrochloride in pharmaceutical preparations for injection (LOD = 960 ng/mL).

Chen and Potter (1994) reviewed determination of lidocaine and MEGX by fluorescence polarization immunoassay (FPIA) and HPLC published in the previous 15 years. HPLC has some advantages over FPIA for dynamic liver function testing. FPIA is also used clinically to check lidocaine serum levels in patients being treated with lidocaine for ventricular arrhythmias. An FPIA method to determine MEGX in highly icteric serum, requiring preliminary precipitation of interfering bilirubin, had an LOD of 8 ng/mL. Results after correction for pre-lidocaine MEGX concentrations were comparable to those obtained by using reversed-phase HPLC with fluorescence detection (Schütz et al., 1998). Reichel et al. (1998) also compared use of FPIA and HPLC to follow lidocaine plasma clearance. The HPLC LODs were 10 ng/mL for lidocaine and 3 ng/mL for MEGX. The FPIA LOD for MEGX was 4 ng/mL.

Lidocaine hydrochloride determination in pharmaceutical preparations may be performed by potentiometric titration using membrane ion-selective electrodes (e.g., Dohnal and Vytras, 1985). Campanella et al. (1998) used a new solid state sensor technology device for potentiometric titration of lidocaine hydrochloride in pharmaceutical preparations at concentrations of 1.0 to 3.7%. The ion-selective (also called ion-sensitive) field effect transistor (ISFET) was prepared from a plasticized poly(vinyl chloride) (PVC) selective membrane and a cocaine reineckate ion exchanger.

Mepivacaine

Heusler (1985) described packed-column GC methods for determination of mepivacaine in blood, serum, plasma, cerebrospinal fluid, and tissue (in most studies, mepivacaine was the internal standard). Capillary GC-MS methods for determining mepivacaine in blood, plasma, and/or urine were described by Ohshima and Takayasu (1999) (LOQ 50 ng/mL) and Watanabe et al. (1998) (LOD ~50 ng/mL). A capillary GC/NPD method could determine mepivacaine in plasma with an LOD of 1 ng/mL (Shen et al., 1998). Ostrea et al. (1998) determined mepivacaine in the meconium of 18 of 98 neonates born in a U.S. hospital using an automated HPLC/UV system and GC/MS.

Escuder-Gilabert et al. (1999) determined mepivacaine in pharmaceutical preparations using HPLC with a liquid micellar mobile phase and UV detection.

Methods using CE for chiral separation were described by Chmela et al. (1985) and Verleysen and Sandra (1998).

Prilocaine

Ohshima and Takayasu (1999) determined prilocaine in human plasma and urine with an LOD of 80 ng/mL and an LOQ of 100 ng/mL using SPE and GC/MS. Another GC/MS method determined prilocaine in human blood with an LOD was about 250 ng/mL. The method used headspace solid-phase microextraction (HS-SPME) for sample cleanup. The mass spectrometer was operated in electron-impact (EI) ionization-SIM mode (Watanabe et al., 1998). Determination of prilocaine in plasma using MMLLE before capillary GC/NPD was more sensitive, with an LOD of 1 ng/mL (Shen et al., 1998).

Klein et al. (1994) used LLE and HPLC/UV to determine EMLA constituents prilocaine and lidocaine and prilocaine metabolite *o*-toluidine simultaneously in plasma using one 200-µL sample. At this volume, the low LOQ was 20 ng/mL for each analyte; the LOD was 4 ng/mL.

Verleysen and Sandra (1998) reviewed CE methods for determination of prilocaine enantiomers in pharmaceuticals.

Ropivacaine

Reif et al. (1998) reviewed recently published (1990-1996) reports on GC and HPLC methods for determining ropivacaine and its metabolites in plasma and other biological media. Two recent GC methods had LODs of 10 and 11 ng/mL in plasma.

Shen et al. (1998) determined ropivacaine in plasma with an LOD of 0.5 ng/mL using MMLLE for sample preparation followed by capillary GC/NPD. Engman et al. (1998) reported that LLE followed by GC/NPD or GC/MS had been used to determine ropivacaine in more than 20,000 samples of plasma, urine, and tissues.

Plasma LODs of HPLC methods reviewed by Reif et al. (1998) for ropivacaine determination ranged from 10 to ~200 ng/mL. Coupling a reversed-phase column with an ion-exchange column allowed ropivacaine determination in plasma ultrafiltrate with an LOD of 3 ng/mL. In a chromatographic system designed for direct injection of plasma, the LOD was 100 ng/mL (Reif et al., 1998).

Halldin et al. (1996) used SPE followed by ion-pair reversed-phase HPLC with UV detection to determine ropivacaine and metabolites in human plasma and urine. Limits of quantitation ranged from 0.3 µM ropivacaine (~70 ng/mL) to about 0.7 µM for 4'-hydroxyropivacaine. The LOD for all metabolites was 0.1 µM. 2,6-Xylidine was not detected. In the more sensitive HPLC/UV method reported by Reif et al. (1998), the LODs for ropivacaine, 3'-hydroxyropivacaine (3'-ROPOH), 4'-hydroxyropivacaine (4'-ROPOH), and PPX were 0.9, 3, 5, and 1 ng/mL, respectively. Because of different physical-chemical properties, separation of the analytes required different extraction procedures and chromatographic conditions.

Supported liquid membrane extraction (SLM) can be used to extract polar compounds from various matrices. An added advantage is the ease of automation. Jönsson et al. (2000) recently described use of SLM with HPLC/UV to determine ropivacaine and metabolites in urine. The method permitted improved extraction selectivity and increased sample throughput. The LODs ranged from 2 nM for 3'-hydroxyropivacaine to 18 nM (~4 ng/mL) for PPX.

HPLC methods for determining ropivacaine and metabolites in hepatic microsomes were described by Oda et al. (1995).

An LC method using columns with immobilized α_1-acid glycoprotein (Chiral AGP column) for chiral separation and determination of ropivacaine and metabolites in urine samples

after LLE was described by Arvidsson et al. (1994). The LOD for (+)-(*R*)-ropivacaine was 2 ng/mL, and the LOD for the (+)-(*R*)- forms of the metabolites was 10 ng/mL. Fawcett et al. (1999) determined ropivacaine and its metabolites in human urine with lower LODs of less than 5 ng/mL using alkaline alcoholic extraction followed by chiral HPLC/UV.

Arvidsson et al. (1999) determined ropivacaine, bupivacaine, and their metabolites in plasma and urine using hydrolysis and SPE for sample preparation followed by ion-pair reversed-phase liquid chromatography (LC) with gradient elution and a UV detector. The LOQ for all analytes in urine samples was 1 µM with LODs usually less than 0.1µM (~25 ng/mL for ropivacaine). The plasma LOQ for all analytes was about 0.1µM.

Yesilada et al. (1998) reviewed chiral methods including CE for separating ropivacaine enantiomers and their determination in pharmaceutical preparations.